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Delivering Discoveries: Expanding the Reach of Precision Medicine

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On behalf of my Associate Editors, Dr. Nathan Pennell and Dr. Hope Rugo, I welcome you to the 2018 ASCO Annual Meeting. It is an honor and privilege to present the 38th volume of the NLM-indexed *ASCO Educational Book*.

The theme of this year’s Meeting is “Delivering Discoveries: Expanding the Reach of Precision Medicine” to highlight the importance of making precision medicine accessible to every patient with cancer. With his presidential theme, Dr. Bruce E. Johnson emphasizes the need to provide improved clinical decision support to providers and enable them to seamlessly stay abreast of genomic information so that they can select the right targeted therapies and treatments for their patients.

This volume contains articles written by Annual Meeting Education Program Faculty and other leaders in oncology who have been invited by the editorial team and Annual Meeting leadership to contribute a manuscript. The majority of articles in the volume are jointly written, thus representing a comprehensive resource for clinicians to supplement and expand learning from the Meeting. Coauthoring a manuscript takes immense planning and collaboration, and I would like to thank all of the authors for their contributions to the 2018 *ASCO Educational Book*.

My heartfelt thanks and eternal gratitude go out to Dr. Pennell and Dr. Rugo for their dedication and camaraderie on this labor of love. I would also like to recognize the expert panel who selflessly dedicated their time to perform thorough and thoughtful peer reviews. Without the effort of many volunteers, we could not ensure each article meets the standards of ASCO and those of an NLM-indexed publication.

It continues to be a highlight of my professional career to extend this invitation to you now, to read the exceptional contributions that comprise this volume. All of the 2018 *ASCO Educational Book* articles, as well as articles from past volumes, are available online at www.asco.org/edbook.

We welcome your feedback and suggestions on how we can improve the content, so please contact us at edbook@asco.org with your comments.

Sincerely,

Don S. Dizon, MD, FACP, FASCO
Editor in Chief
INVITED ARTICLES

This year’s invited articles represent the 2018 ASCO Annual Meeting theme, “Delivering Discoveries: Expanding the Reach of Precision Medicine.” These important contributions to the 38th volume of the ASCO Educational Book emphasize the need to enhance clinical decision-making for providers so that they may stay current on genomic information to select the best targeted therapies for their patients.

Authors were nominated by the ASCO Educational Book Editors and 2018 Annual Meeting leadership, and authors developed their topics under the guidance of Dr. Hope S. Rugo, Associate Editor.

ARTICLES

Predicting and Preventing Anthracycline-Related Cardiotoxicity
Saro Armenian and Smita Bhatia

Gastrointestinal and Hepatic Toxicities of Checkpoint Inhibitors: Algorithms for Management
Shilpa Grover, Osama E. Rahma, Nikroo Hashemi, and Ramona M. Lim

Cancer of Unknown Primary Site: New Treatment Paradigms in the Era of Precision Medicine
John D. Hainsworth and F. Anthony Greco
Anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin) are among the most potent chemotherapeutic agents and have truly revolutionized the management of childhood cancer. They form the backbone of chemotherapy regimens used to treat childhood acute lymphoblastic leukemia, acute myeloid leukemia, Hodgkin lymphoma, Ewing sarcoma, osteosarcoma, and neuroblastoma. More than 50% of children with cancer are treated with anthracyclines. The clinical utility of anthracyclines is compromised by dose-dependent cardiotoxicity, manifesting initially as asymptomatic cardiac dysfunction and evolving irreversibly to congestive heart failure. Childhood cancer survivors are at a five- to 15-fold increased risk for congestive heart failure compared with the general population. Once diagnosed with congestive heart failure, the 5-year survival rate is less than 50%. Prediction models have been developed for childhood cancer survivors (i.e., after exposure to anthracyclines) to identify those at increased risk for cardiotoxicity. Studies are currently under way to test risk-reducing strategies. There remains a critical need to identify patients with childhood cancer at diagnosis (i.e., prior to anthracycline exposure) such that noncardiotoxic therapies can be contemplated.
controls. There was also a higher prevalence of diabetes (23% vs. 14%), dyslipidemia (9% vs. 6%), and multiple (two or more) cardiovascular risk factors (27% vs. 22%). Of note, hypertension had the strongest modifying effect on risk for CHF; anthracycline-exposed survivors who developed de novo hypertension had a 12.4-fold (95% CI, 7.5–20.1) higher risk for CHF compared with those without hypertension. Important, the combined effect of anthracycline exposure plus hypertension resulted in potentiation of CHF risk that exceeded the additive effect of each variable alone. This information provides much-needed insight into the development of novel preventive approaches to reduce CHF risk, as discussed later.

**Genetic Risk Factors**

However, despite an established dose-dependent association, there is interpatient variability in risk for CHF for exposure to anthracycline at any dose, such that clinical variables alone yield moderate predictive power in detecting CHF. The pathophysiology of cardiotoxicity is unclear, but it is thought to be mediated by the generation of reactive oxygen species following anthracycline exposure and resultant DNA damage. A considerable amount of research has contributed to our understanding of genetic susceptibility to anthracycline-related cardiotoxicity. Systematic reviews have detailed results of studies reporting genetic associations in cancer survivor populations. Polymorphisms in adenosine triphosphate–binding cassette transporter (ABC) genes are associated with anthracycline-related cardiomyopathy. ABC transporters play a role in multidrug resistance via active cellular efflux of drugs, including anthracyclines. Reduced activity may therefore lead to intracellular anthracycline accumulation and resultant cellular toxicity. Variants in this family of genes replicated in childhood cancer survivor cohorts include ABCC5 (A-1629T, rs7627754), associated with substantial reductions in ejection and shortening fractions in survivors homozygous for the T allele, as well as ABCB4 (rs4148808), a gender-dependent association significant in female patients. In addition, a variant in histamine N methyltransferase HNMT (rs17583889) confers risk only in younger children exposed to anthracyclines. Another study found a significant association between cardiac compromise and a nonsynonymous coding variant in the RARG gene (S427L, rs2229774). In animal models, RARG binds to and regulates expression of topoisomerase II and is highly expressed in cardiac tissue. In correlative biology studies, the investigators were able to show that this RARG variant impaired RARG repression of topoisomerase IIβ in vitro, thus potentially rendering cells more susceptible to the cytotoxic effect of anthracyclines. Studies in childhood cancer survivors found associations between anthracycline-related cardiotoxicity and variants in soluble carrier transporters (SLC28A3, SLC22A17, and SLC22A7)36-38; these findings were successfully replicated. Studies have also demonstrated an increased risk conferred by variation in a gene within the glucuronosyltransferase family, UGT1A6. These enzymes act by glucuronidation of a variety of drugs. The variant is indicative of the UGT1A6*4 haplotype, also reported to result in a 30% to 100% reduction in enzyme activity. Several studies have demonstrated genetic variants to serve as modifiers of the dose-dependent increase in risk for cardiomyopathy (Table 1). Carboxyl reductases (CBRs) catalyze reduction of anthracyclines to cardiotoxic alcohol.
metabolites. Polymorphisms in CBR influence synthesis of these metabolites. Among childhood cancer survivors, homozygosity for G allele in CBR3 contributed to increased cardiomyopathy risk associated with low- to moderate-dose anthracyclines, such that there seemed to be no safe dose for patients homozygous for the CBR3 V244M G allele (Fig. 2). A recent study demonstrated a gene-environment interaction between single-nucleotide polymorphism (SNP) rs1786814 on the CELF4 gene and higher doses of anthracyclines (Fig. 3). This association was replicated in an independent survivor cohort. CELF4 protein is responsible for premRNA alternative splicing of TNNT2. Myofilaments with two or more variants of TNNT2 demonstrate irregular contractile response to intracellular calcium ion concentration, resulting in decreased ventricular pumping efficiency. The investigators demonstrated the presence of an embryonic TNNT2 splicing variant in cardiac tissue from carriers homozygous for the CELF4 variant shown to be associated with an increased risk for dilated cardiomyopathy. Another study used a carefully curated SNP array (IBC array) that included 2,100 genes associated with de novo cardiovascular disease and found SNP rs2223888 on HAS3 gene to be associated with an increased risk for cardiomyopathy at high doses of anthracyclines (Fig. 4). The SNP was replicated in an independent cohort. In addition, using heart tissue from a healthy cohort, the investigators found that the gene expression was lower among those with the high-risk allele. HAS3 encodes hyaluronic acid, an antioxidant. Thus, lower gene expression by the high-risk allele would suggest higher reactive oxygen species after anthracycline exposure and hence a higher risk for cardiomyopathy. A recent study interrogating candidate SNPs was able to replicate the previously reported association between UGT1A6 rs17863783 CELF4 variant (rs1786814) and HAS3 (rs2232228) and cardiotoxicity.

**PREDICTING RISK FOR ANTHRACYCLINE-RELATED CARDIOTOXICITY**

As discussed previously, important risk factors for anthracycline-related CHF include anthracycline dose, chest radiation, presence of conventional cardiovascular risk factors, and, in some studies, age at initial cancer diagnosis and sex. Given the high incidence of and poor outcomes after anthracycline-related CHF, anthracycline-exposed survivors may benefit from customized and validated risk prediction models. Leveraging the resources offered by the Childhood Cancer Survivor Study (CCSS) cohort, the investigators created a clinically useful model that incorporated demographic and cancer treatment information available at the end of therapy to predict subsequent CHF risk with reasonable discrimination among 5-year survivors and then validated the resulting risk scores in two external cohorts. CCSS participants free of substantial cardiovascular disease 5 years after cancer diagnosis (13,060 participants) were observed through age 40 for the development of CHF. More than 4,000 siblings were used to establish the baseline population risk. An additional 3,421 survivors from Emma Children’s Hospital (Amsterdam, the Netherlands), the National Wilms Tumor Study, and the St. Jude Lifetime Cohort Study were used to validate the CCSS prediction models. CHF was reported by 285 CCSS participants. Risk scores on the basis of selected exposures (sex, age at cancer diagnosis, and anthracycline and chest radiotherapy doses) achieved an area under the curve of 0.74 and a concordance statistic of 0.76 at 40 years. The areas under the curve for the validation cohorts ranged from 0.68 to 0.82. Risk scores were collapsed to form low-, moderate-, and high-risk groups, corresponding to cumulative incidence of CHF at age 40 of 0.5% (95% CI, 0.2%–0.8%), 2.4% (95% CI, 1.8%–3.0%), and 11.7% (95% CI, 8.8%–14.5%), respectively. The development of a robust CHF prediction model for this population may help clinicians

### TABLE 1. Anthracycline-Induced Cardiotoxicity-Related Pharmacogenetic Variants

<table>
<thead>
<tr>
<th>Gene</th>
<th>rs</th>
<th>Biologic Process</th>
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<tbody>
<tr>
<td>ABCB1</td>
<td>rs1128503</td>
<td>Drug transport</td>
</tr>
<tr>
<td>ABC1</td>
<td>rs45511401</td>
<td>Drug transport</td>
</tr>
<tr>
<td></td>
<td>rs60782127</td>
<td>Drug transport</td>
</tr>
<tr>
<td></td>
<td>rs4148356</td>
<td>Drug transport</td>
</tr>
<tr>
<td>CAT</td>
<td>rs10836235</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>CBR3</td>
<td>rs8133052</td>
<td>Drug metabolism</td>
</tr>
<tr>
<td>NCF4</td>
<td>rs1800566</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>NQO1</td>
<td>rs1800566</td>
<td>Energy use</td>
</tr>
<tr>
<td>NR1/2</td>
<td>NA</td>
<td>Regulation of drug metabolism and/or transport and apoptosis</td>
</tr>
<tr>
<td>RARG</td>
<td>rs2229774</td>
<td>Derepression of the key genetic determinant Top2b, increasing oxidative stress</td>
</tr>
<tr>
<td>SLC22A16</td>
<td>rs714368</td>
<td>Increased drug exposure</td>
</tr>
<tr>
<td>TOP2A</td>
<td>NA</td>
<td>DNA regulation</td>
</tr>
<tr>
<td>HAS3</td>
<td>rs2232228</td>
<td>Oxidative stress</td>
</tr>
<tr>
<td>CELF4</td>
<td>rs1786814</td>
<td>Expression of abnormally spliced TNNT2 variants</td>
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Abbreviations: rs, reference single-nucleotide polymorphism cluster number; NA, not applicable.
refine surveillance strategies to better identify and counsel patients at higher risk for future events.

A second study used genetic variants, in addition to clinical and genetic factors, to identify those at highest risk for anthracycline-related cardiotoxicity. They evaluated 2,977 SNPs in 220 key drug biotransformation genes in a discovery cohort of 156 anthracycline-treated children from British Columbia, with replication in a second cohort of 188 children from across Canada and further replication of the top SNP in a third cohort of 96 patients from Amsterdam, the


Patients with no exposure to anthracyclines and carrying CBR3:GA/AA genotype served as the reference group. Magnitude of risk is expressed as odds ratio, which was obtained using conditional logistic regression adjusting for age at diagnosis, sex, and chest radiation. Cumulative anthracycline dose is expressed as doxorubicin equivalent.

FIGURE 3. Risk for Cardiomyopathy by Anthracycline Dose and CELF4 Genotype Status (AA, GA, GG)

Odds ratios were calculated on the basis of model 2, which treated anthracycline dose as a continuous variable (reference group, AA genotype with no anthracycline exposure). Cumulative anthracycline dose is expressed as doxorubicin equivalent.
Netherlands. They explored combining multiple variants into a single prediction model together with clinical risk factors and classification of patients into three risk groups. In the high-risk group, 75% of patients were accurately predicted to develop cardiotoxicity, with 36% developing this within the first year alone, whereas in the low-risk group, 96% of patients were accurately predicted not to develop cardiotoxicity. This study demonstrated that combined with clinical risk factors, genetic risk profiling might be used to identify high-risk patients who can then be provided with safer treatment options.36

RISK REDUCTION STRATEGIES
Identifying patients at high risk for CHF begs the availability of effective interventions that could be applied to newly diagnosed children with cancer or to cancer survivors. We describe examples of interventions below.

Newly Diagnosed Patients: Therapeutic Modifications
The cumulative anthracycline exposure in contemporary therapeutic protocols ranges between 75 and 450 mg/m² (Table 2). However, currently, there are no plans for reduction in anthracycline dose in the foreseeable future. Nonetheless, there is a strong desire to consider alternative therapies if patients at very high risk for CHF were to be identified. If anthracyclines cannot be avoided, several strategies to decrease the risk of CHF have been proposed: (1) less cardiotoxic analogs: in adults, liposomal-encapsulated doxorubicin is favored over conventional doxorubicin, but pediatric randomized controlled trial (RCT) data are lacking; (2) longer anthracycline infusion duration: although an infusion duration of at least 6 hours has been shown to be cardioprotective in adults, RCTs in children have not identified a protective effect; and (3) cardioprotective agents: dexrazoxane (ICRF-187) is the only U.S. Food and Drug Administration–approved cardioprotective agent. The mechanisms of action include iron chelation, reduction in reactive oxygen species formation, and topoisomerase II inhibition. Although dexrazoxane is associated with reduction in CHF risk (relative risk, 0.43; p < .001), there is a nonsignificant increase in risk for subsequent malignant neoplasms (relative risk, 2.4; p = .06). Concurrent use of etoposide with dexrazoxane may increase the risk of therapy-related acute myeloid leukemia, whereas concurrent cranial radiation use may increase the risk for subsequent brain tumors. The general consensus is that a decision to use dexrazoxane in children should balance the risks of CHF and subsequent malignant neoplasms. An ongoing study (NCT0179012) is examining the long-term (> 10 years) efficacy of dexrazoxane in survivors treated on RCTs across a range of anthracycline exposures (100–360 mg/m²).

Childhood Cancer Survivors: Screening Recommendations for Early Detection of Anthracycline-Related CHF
In anthracycline-treated childhood cancer survivors, there is often a long latency between asymptomatic cardiac dysfunction and clinically evident CHF. Subtle changes in cardiac function can be detected long before declines in
more established measures of cardiac function such as left ventricular (LV) ejection fraction (EF).\textsuperscript{52} In a recent cross-sectional study of more than 1,800 10-year survivors of childhood cancer treated with anthracyclines and/or radiation, only 5.8% of participants had LV EFs less than 50%.\textsuperscript{53} However, nearly one-third (28%) had cardiac dysfunction, as measured by global longitudinal strain, a novel and prognostic echocardiographic measure of systolic function, and 17.6% had reduced exercise capacity, as determined by a 6-minute walk test (abnormal, < 490 m).\textsuperscript{53} In another study of anthracycline-treated survivors with normal LV EFs,\textsuperscript{54} there were dose-dependent changes in LV chamber diameter and wall thickness, resulting in an increase in LV end-systolic wall stress, a prognostic marker of CHF risk in nononcology populations. These echocardiographic LV indices can be readily obtained from standard echocardiograms obtained as part of clinical care, allowing the implementation of screening and prevention strategies in survivors at highest risk for developing therapy-related CHF.

With this in mind, the Children’s Oncology Group has developed the Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancer (www.survivorshipguidelines.org). The primary goal is early detection of treatment-related complications (including anthracycline-related CHF) in childhood cancer survivors.\textsuperscript{55} Given that screening recommendations are consensus based, a critical appraisal into their cost-effectiveness is imperative. Two recent studies\textsuperscript{56,57} used simulation Markov modeling to determine the cost-effectiveness of the Children’s Oncology Group guideline recommendations. They compared lifetime costs, quality-adjusted life-years, and total risk for CHF for different screening intervals versus no screening in hypothetical populations of childhood cancer survivors. These studies suggest that routine surveillance per the current Children’s Oncology Group guidelines is cost-effective and may reduce the incidence of CHF, with the greatest benefits seen in survivors treated with high-dose (≥ 250 mg/m\textsuperscript{2}) anthracyclines.

The Children’s Oncology Group guidelines recently contributed to the International Late Effects of Childhood Cancer Guideline Harmonization Group, yielding uniform guidelines for cardiac screening.\textsuperscript{58} Routine surveillance with echocardiography is recommended for survivors at high risk for CHF, defined as those with anthracycline exposure of 250 mg/m\textsuperscript{2} or greater or chest radiotherapy at 35 Gy or greater or lower dose (≥ 100 mg/m\textsuperscript{2}) anthracyclines plus chest radiotherapy.\textsuperscript{58} Screening should begin no later than 2 years after anthracycline exposure and be repeated a minimum of every 5 years thereafter. More frequent screening may be performed according to level of risk and clinical index of suspicion. Cardiology consultation is strongly recommended for those noted to have cardiac dysfunction.\textsuperscript{58}

Recent studies have examined whether the use of noncardiographic imaging\textsuperscript{59,60} and blood-based biomarkers\textsuperscript{61,62} may improve the screening yield in survivors. In nononcology populations at risk for CHF (e.g., after myocardial infarction), cardiac magnetic resonance imaging can provide accurate and important information regarding cardiac health and function.\textsuperscript{63} Cardiac magnetic resonance imaging has therefore been the focus of several population-based screening studies in survivors of childhood and adult-onset cancers.\textsuperscript{64,65} These studies have highlighted its high sensitivity and specificity, noninvasiveness, and avoidance of ionizing radiation. Yet despite these features, the cost and limited availability of cardiac magnetic resonance imaging precludes its widespread use for population-based screening of asymptomatic disease.\textsuperscript{66} For now, screening with two-dimensional echocardiography remains the standard of care, with consideration of cardiac magnetic resonance imaging for individuals in whom echocardiography is not technically feasible or optimal.\textsuperscript{58} With respect to blood biomarkers of cardiac injury and remodeling, studies have suggested that elevated cardiac troponins and natriuretic peptide levels during anthracycline exposure can be associated with the development of cardiac dysfunction in the first 3 years after treatment,\textsuperscript{67,68} but the association between these early

### Table 2. Use of Anthracyclines in Contemporary Childhood Cancer Therapeutic Protocols

<table>
<thead>
<tr>
<th>Primary Cancer</th>
<th>Anthracycline Dose (mg/m²)*</th>
<th>Plans for Reduction in Anthracycline Dose for All Patients</th>
<th>Alternative Therapeutic Options if Patient Is at High Risk for CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>75–225</td>
<td>No plans for reduction in dose across the board</td>
<td>May consider alternative therapies on a case-by-case if a patient is at very high risk for CD</td>
</tr>
<tr>
<td>AML</td>
<td>450</td>
<td>No plans for reduction in dose across the board</td>
<td>May consider alternative therapies on a case-by-case basis if a patient is at very high risk for CD</td>
</tr>
<tr>
<td>HL</td>
<td>250</td>
<td>No plans for reduction in dose across the board</td>
<td>May consider lowering anthracycline dose for patients at very high risk for CD; would need to add agents that could cause other toxicities</td>
</tr>
<tr>
<td>ES</td>
<td>375</td>
<td>No plans for reduction in dose across the board</td>
<td>No alternative treatment; focus on aggressive screening/pharmacologic interventions for those at very high risk for CD</td>
</tr>
<tr>
<td>OS</td>
<td>450</td>
<td>No plans for reduction in dose across the board</td>
<td>May consider noncardiotoxic drugs if at high risk for CD (slightly inferior survival)</td>
</tr>
<tr>
<td>NBL</td>
<td>300</td>
<td>No plans for reduction in dose across the board</td>
<td>For patients at very high risk for CD, would reserve anthracyclines only if the patients do not respond to other treatments on a case-by-case basis</td>
</tr>
</tbody>
</table>

*Cumulative anthracycline exposure in contemporary therapeutic protocols; dose expressed as doxorubicin equivalent.\textsuperscript{51}

Abbreviations: CD, cardiovascular disease; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HL, Hodgkin lymphoma; ES, Ewing sarcoma; OS, osteosarcoma; NBL, neuroblastoma.
findings and subsequent CHF is less clear. Data regarding the use of these blood biomarkers in childhood cancer survivors who are years removed from their primary treatment has been mixed, as high negative predictive values (63%–100%) but low sensitivity (0%–32%) and low positive predictive values (12.5%–37.5%) make them unreliable for use as the only surveillance strategy in this population.\(^{52,58}\)

Despite the existence of well-established cardiac screening recommendations, the period of time when childhood cancer survivors are at the greatest risk for CHF also corresponds to the time when their level of engagement in risk-based screening is the lowest.\(^{69}\) Fewer than 30% of long-term survivors (> 5 years from diagnosis) undergo routine risk-based echocardiographic screening,\(^{70}\) despite the fact that nearly 90% report receiving regular general medical care,\(^{70-72}\) suggesting that long-term survivorship care is largely provided in the primary care setting. The growing number of childhood cancer survivors requiring care in future years and the capacity pressures facing primary cancer centers are strong drivers for examining new approaches to screening and survivorship care delivery. In this context, mobile health technology may bridge the gap in survivorship care delivery, especially as it pertains to screening for cardiovascular disease.\(^{73,74}\) A recent study demonstrated that a handheld noninvasive wireless device can accurately determine LV EF in nononcology patients with chronic CHF, providing real-time information on cardiac function for remote clinical management.\(^{74}\) Studies examining similar screening mobile health platforms in childhood cancer survivors are ongoing and when completed may lead to a paradigm shift in disease prevention and early detection in individuals at high risk.

**Survivors: Interventions to Reduce Anthracycline-Related CHF**

Strategies for prevention of CHF in survivors who have already been exposed to anthracyclines have mostly been adapted from studies in adults with asymptomatic cardiac dysfunction due to causes other than anthracyclines. These include early initiation of medications (e.g., angiotensin-converting enzyme inhibitors, β-blockers) to prevent the progression from asymptomatic to symptomatic disease.\(^{61}\) However, there are few studies conducted in childhood cancer survivors to guide which pharmacologic agents, if any, should be used once asymptomatic cardiac dysfunction has been detected. A retrospective study in 18 anthracycline-treated survivors showed that although enalapril (an angiotensin-converting enzyme inhibitor) improved LV structure and function in individuals with cardiac dysfunction,\(^{75}\) this was short lived. A subsequent RCT in anthracycline-treated childhood cancer survivors assessed the effectiveness of enalapril versus placebo in survivors with normal LV EFs but at high risk for CHF because of a history of cardiac dysfunction.\(^{76}\) The study failed to show an impact on its primary outcome (myocardial contractility index), but there was improvement in other cardiac measures (LV end-systolic wall stress). Because β-blockers may be more likely to reverse the chronic cardiac remodeling than angiotensin-converting enzyme inhibitors,\(^{77}\) an ongoing RCT (NCT02717570) is assessing the impact of the β-blocker carvedilol on prognostic markers of LV remodeling in individuals treated with high-dose (≥ 250 mg/m²) anthracyclines.\(^{78}\)

Aggressive management of comorbidities such as hypertension and diabetes may be the most practical approach to reducing long-term CHF risk, but there is a paucity of information on optimal strategies for screening and intervention in at-risk survivors. An ongoing RCT (NCT03104545) is addressing this gap in knowledge in a systematic fashion. Survivors will first undergo screening to determine the prevalence of underdiagnosis and undertreatment of these health conditions. Individuals who are found to be underdiagnosed or undertreated will be randomized to a survivorship care plan with counseling to improve control of these risk factors or to a survivorship care plan alone (no counseling); efficacy will be measured through objective assessments of cardiometabolic risk (e.g., blood pressure, blood cholesterol, glucose). Additionally, health behaviors (e.g., exercise, diet) may be as important to address in survivors as conventional risk factors. In survivors of childhood Hodgkin lymphoma, vigorous exercise has been associated with a lower risk for cardiovascular disease in a dose-dependent manner\(^{79}\) and should be encouraged in all cancer survivors per established guidelines.\(^{58,80}\) Studies (e.g., NCT02244411 and NCT03223753) are currently under way to improve adherence to these lifestyle and behavior recommendations.

In conclusion, anthracyclines increase the risk of cardiomyopathy in a dose-dependent fashion. Age at exposure, sex, chest radiation, cardiovascular risk factors and genomic variants modify this dose-response relation. Prediction models have been developed for childhood cancer survivors to identify those at increased risk for cardiotoxicity. Studies are currently under way to test risk-reducing strategies. However, there is a critical need to identify patients with childhood cancer at diagnosis (i.e., prior to anthracycline exposure) such that noncardiotoxic therapies can be contemplated.

**References**


Immune checkpoint inhibitors are an important part of the treatment armamentarium for patients with a number of different cancers. Since initial approval of the anti–CTLA-4 antibody ipilimumab for the treatment of metastatic melanoma, indications for immune checkpoint inhibitor therapy have been expanding. Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have also shown antineoplastic activity in several tumor types. One or more of the anti–PD-1 monoclonal antibodies (nivolumab, pembrolizumab) and monoclonal antibodies to PD-L1 (durvalumab, atezolizumab) have shown efficacy in metastatic melanoma, non–small cell lung carcinoma, renal cell carcinoma, urothelial carcinoma, Hodgkin lymphoma, mismatch repair–deficient solid tumors, hepatocellular carcinoma, head and neck carcinoma, and Merkel cell (neuroendocrine) carcinoma.

MECHANISM OF ACTION AND TOXICITY

Antineoplastic activity of these agents results from their effect on immune checkpoints that normally serve to dampen the immune response and protect against detrimental inflammation and autoimmunity. Normally, interaction between B7.1 or B7.2 on antigen-presenting cells and CD28 on the T cell results in T-cell activation. CTLA-4 is constitutively expressed on inhibitory CD4+ CD25+ regulatory T cells and has a high affinity receptor for B7.1 and B7.2. CTLA-4 attenuates T-cell response after antigenic stimulation by competing with CD28 for binding to B7.1 and B7.2, thereby blocking T-cell activation and signaling for inhibition of cell cycle progression and cytokine production. Monoclonal antibodies against CTLA-4 can lead to expansion of tumor-specific T cells and to tumor destruction. PD-1 is upregulated on activated T cells, and on recognition of tumor via the T-cell receptor, PD-1 engagement by PD-L1 can result in T-cell inactivation. Anti–PD-1/PD-L1 antibodies block the interaction between PD-1 receptor and its ligands, thereby disrupting signals that result in T-cell inactivation.

Although monoclonal antibodies against CTLA-4 and PD-1/PD-L1 augment T cell–specific immune response, resulting in antitumor activity, this can also lead to a range of systemic and organ-specific side effects because of an unchecked immune response. Patients with moderate to severe immune-related adverse events usually require interruption of the checkpoint inhibitor and immunosuppression. Although such interruption in ongoing treatment and the use of immunosuppression have not been associated with reduced survival, the toxicities themselves may be severe and can impact quality of life. In addition, delays in diagnostic evaluation and/or nonadherence to treatment have been associated with fulminant disease.1

EPIDEMIOLOGY

Most immune-related adverse events appear within 1–2 months after the start of treatment. However, in some cases, they occur several months after starting or completing treatment.2 Among checkpoint inhibitors, the incidence of immune-related adverse events with anti–PD-1 or anti–PD-L1 monoclonal antibodies seems to be lower compared with anti–CTLA-4 antibodies, and adverse events are less severe.
In phase III trials, the incidence rates of immune-related adverse events in patients treated with single-agent anti–CTLA-4 antibodies and patients treated with anti–PD-1/PD-L1 antibodies were up to 72% and 25%, respectively. Diarrhea/colitis and hepatitis are among the most common adverse events leading to discontinuation of immune checkpoint inhibitors. Hepatitis rates are similar in patients treated with anti–CTLA-4 and anti–PD-1 antibodies; however, diarrhea and colitis are more frequent with CTLA-4 blocking antibodies. Patients treated with a combination of anti–CTLA-4 and anti–PD-1/PD-L1 antibodies develop more frequent and severe toxicities compared with monotherapy with these drugs. However, the spectrum of immune-related adverse events is not unique to combination therapy.

DIARRHEA/COLITIS

Diarrhea is a frequent adverse effect of checkpoint inhibitor therapy. The term “colitis” encompasses abdominal pain or endoscopic/radiologic evidence of colonic inflammation. In clinical trials of patients treated with ipilimumab, the incidence rates of diarrhea and colitis are 23% to 33% (grade 3/4, 3%–6%) and 8% to 12% (grade 3/4, 7%–9%), respectively (Table 1). Patients treated with PD-1/PD-L1 blockade have lower incidence rates of diarrhea (11%–19%) and colitis (1%–4%), and the symptoms are usually milder, with grade 3/4 diarrhea/colitis in approximately 1% to 3%. The incidence of diarrhea and colitis are highest with the combination of anti–CTLA-4 and anti–PD-1/PD-L1 antibodies, with rates of up to 45% (grade 3/4, 9%–11%) and 26% (grade 3/4, 8%–17%), respectively, in clinical trials in which patients were treated with both ipilimumab and nivolumab. Nonsteroidal anti-inflammatory drug use may increase the risk of ipilimumab-induced colitis.

Clinical Presentation

Immune-related diarrhea secondary to checkpoint inhibitor therapy is usually a consequence of underlying colonic inflammation. Approximately one-third of patients have concomitant enteritis, but in rare cases, patients may present with diarrhea caused by enteritis alone. Patients usually present with frequent nonbloody stools associated with urgency. Bloody diarrhea is rare. In patients with concurrent upper gastrointestinal tract involvement, nausea, vomiting, early satiety, and bloating may be present. The median onset of diarrhea is approximately 6 to 8 weeks after initiation of therapy.

Diagnostic Evaluation

The evaluation of diarrhea is based on the duration, severity, and presence of alarm features that may warrant hospitalization (Fig. 1 and Table 2). Patients treated with immune checkpoint blockade have a low risk of developing serious infection in the absence of corticosteroids and/or tumor necrosis factor-alpha inhibitor use. However, it remains important to rule out an underlying infectious etiology (Table 2).

Laboratory Studies

Fecal lactoferrin or calprotectin can be used as a surrogate measure for fecal leukocytes and intestinal inflammation. We routinely obtain stool cultures for bacterial pathogens and additional stool testing for Clostridium difficile infection, rotavirus, and norovirus. In addition, specific testing for Escherichia coli O157:H7/shiga toxin should be performed. Testing for ova and parasites, Cryptosporidium, and Giardia is warranted in patients with risk factors or recent travel to endemic areas. Laboratories routinely identify Salmonella, Shigella, and Campylobacter on stool cultures, but isolation for Yersinia, Vibrio, and Aeromonas, if suspected, must be specified (Table 2). If a multiplex molecular panel is performed for microbiologic stool testing, positive test results must be confirmed with stool cultures. These assays can detect genetic material that does not necessarily indicate an active infection.

Abdominal Imaging

Abdominal imaging is not routinely required in patients with mild (grade 1) diarrhea but can provide clinically useful information in patients with more severe symptoms or abdominal pain. Abdominal CT findings in patients with checkpoint inhibitor colitis include mesenteric vessel engorgement, marked thickening of the bowel wall, mucosal hyperenhancement, and a fluid-filled colon. Three distinct patterns of colon inflammation have been described: diffuse colitis pattern with diffuse colonic wall thickening, segmental

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TABLE 1. Incidence and Severity of Checkpoint Inhibitor–Related Gastrointestinal and Hepatic Toxicity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diarrhea</th>
<th>Colitis</th>
<th>Hepatic Transaminase Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Timing of onset, weeks</td>
<td>Any Grade, %</td>
<td>Grade 3/4, %</td>
<td>Any Grade, %</td>
</tr>
<tr>
<td>6–8</td>
<td>23–33</td>
<td>11–19</td>
<td>44–45</td>
</tr>
<tr>
<td>Anti–CTLA-4 mono-therapy</td>
<td>3–6</td>
<td>1–3</td>
<td>9–11</td>
</tr>
<tr>
<td>Anti–PD-1/PD-L1 mono-therapy</td>
<td>8–12</td>
<td>12–26</td>
<td>8–17</td>
</tr>
<tr>
<td>Combination anti–CTLA-4 and anti–PD-1/PD-L1</td>
<td>7–9</td>
<td>3–10</td>
<td>6–19</td>
</tr>
</tbody>
</table>
coliți s associated with diverticulosis, and isolated rectosigmoid coliți s without diverticulosis.21 Findings on abdominal CT scan are not specific for checkpoint inhibitor coliți s; however, imaging can rule out complications, including bowel perforation, abscess, and toxic megacolon.22

**Endoscopy**

All patients with bloody diarrhea and those with nonbloody diarrhea that is persistent or grade 2 or worse diarrhea should undergo endoscopic evaluation. Endoscopic evaluation serves to rule out other etiologies (e.g., cytomegalovirus infection, ischemic coliți s in the setting of dehydration), and it can establish the diagnosis of checkpoint inhibitor coliți s and guide therapy. Although a flexible sigmoidoscopy with biopsies of the left colon can be diagnostic in approximately 95% of suspected ipilimumab-induced coliți s cases, it is unclear if this is adequate in patients with PD-1/PD-L1 inhibitor toxicity given that patients may have enteritis alone.16

Ipilimumab-induced coliți s can result in a continuous pattern of colonic inflammați on. The endoscopic appearance is nonspecific with mucosal edema, erythema, and diffuse but shallow ulcers.15 Small intestinal and colonic inflammați on with PD-1/PD-L1 inhibitors appears to be much less prominent

![Diagram of Approach to the Evaluation and Management of Checkpoint Inhibitor Colitis/Diarrhea](https://ascopubs.org/doi/abs/10.1200/JTO.2018.000020)

**TABLE 2. Checklist for Evaluation of Patients With Presumed Checkpoint Inhibitor Colitis**

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Patient Characteristics</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory studies</td>
<td>Grade 1–4 diarrhea</td>
<td>Stool bacterial cultures (Salmonella, Shigella, Campylobacter) and testing for E. coli O157:H7/shiga toxin; additional stool tests: stool lactoferrin, C. difficile, rotavirus and norovirus</td>
</tr>
<tr>
<td></td>
<td>Grade 1–4 diarrhea with risk factors (e.g., travelers’ diarrhea, ongoing outbreak, seafood or shellfish exposure)</td>
<td>Vibrio, Aeromonas, Listeria, Yersinia, Cryptosporidium stool antigen, ova, and parasites (microscopy, stool antigen, or molecular testing), Giardia stool antigen</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Grade 2–4 diarrhea</td>
<td>Flexible sigmoidoscopy or colonoscopy; upper endoscopy may be indicated in selected patients with upper gastrointestinal symptoms (e.g., bloating, epigastric pain)</td>
</tr>
<tr>
<td>Imaging</td>
<td>Grade 2 diarrhea and abdominal pain; grade 3–4 diarrhea</td>
<td>Abdominal CT scan</td>
</tr>
</tbody>
</table>

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&middot; Abbreviations: ADL, activities of daily living; CTCAE, Common Terminology Criteria for Adverse Events; PCR, polymerase chain reaction; TB, tuberculosis; TNF, tumor necrosis factor.
Development of diarrhea and/or colitis during use of one checkpoint inhibitor does not necessarily prohibit the use of another. Treatment with nivolumab after ipilimumab seems to be safe. In a retrospective study of 576 nivolumab-treated patients, of which 312 patients (54%) had received prior ipilimumab therapy, the incidence rates of treatment-related adverse events (any grade and grade 3–4) in the overall population were similar to those among patients who had received prior ipilimumab.

HEPATOTOXICITY

Hepatotoxicity with checkpoint inhibitors usually results in a transaminitis, with elevations of aspartate aminotransferase and alanine aminotransferase and, less commonly, hyperbilirubinemia. Patients usually present with asymptomatic elevations in transaminases; however, some patients may have an associated fever, fatigue, or jaundice. In rare cases, fulminant hepatitis has been reported. The onset of hepatitis with immunotherapy is usually 8 to 12 weeks after initiation of treatment. However, elevations as early as 8 days and up to 21 months after initiation of treatment have also been reported. Hepatitis occurs in up to 1% to 7% of patients during monotherapy with ipilimumab and 1% to 6% of patients treated with anti–PD-1/PD-L1 antibodies nivolumab or pembrolizumab. Rates of grade 3 or 4 toxicity are lower (1%–3%; Table 1). However, the incidence of toxicity is higher in patients treated with combination therapy (13%–30%, of which 6%–19% is ≥ grade 3).

Patients being treated with immunotherapy require monitoring of liver tests before therapy. Similar to patients with other immune-related adverse events, diagnostic evaluation should rule out other alternative etiologies (Fig. 2). Imaging in patients with elevated liver tests serves to rule out partial bile duct obstruction from choledolithiasis, the presence of metastatic disease, and vascular obstruction, which may cause elevations in liver tests. Imaging with abdominal CT or ultrasound may be normal in mild cases of checkpoint inhibitor hepatitis. However, in more severe cases, hepatomegaly, periportal edema, attenuated liver parenchyma, and periporal lymphadenopathy may be present. Histologic changes associated with ipilimumab-induced hepatitis include a pattern of hepatocellular injury with panlobular hepatitis, but bile duct injury has also been reported. Histologic changes in ipilimumab-related hepatitis are not specific and may be seen in patients with acute viral and autoimmune hepatitis.

Hepatitis usually responds to the use of corticosteroids. However, the time to resolution is approximately 8 weeks, and relapses are frequent as corticosteroids are tapered. It is unclear if the use of N-acetylcysteine or ursodeoxycholic acid can hasten normalization of liver tests and if budesonide has a role in the treatment of patients with hepatotoxicity. Infliximab does not have a role in the treatment of checkpoint inhibitor hepatitis because of the risk of hepatotoxicity associated with tumor necrosis factor-alpha inhibitors. Mycophenolate mofetil and tacrolimus have also been used in steroid-refractory cases. In a case report, treatment with antithymocyte globulin resulted in resolution of hepatitis in
a patient with checkpoint inhibitor–induced hepatitis that was refractory to treatment with mycophenolate mofetil and steroids.31

PANCREATIC ENZYME ELEVATION AND PANCREATITIS

Although the incidence of acute pancreatitis is low, elevation in pancreatic enzymes without evidence of pancreatitis is noted in a number of patients treated with checkpoint inhibitors (10%–15% grade 3/4 enzyme elevation).32 In a retrospective study of 119 patients with melanoma treated with nivolumab and ipilimumab, 10 (8%) had grade 3 or worse amylase, 32 (27%) had grade 3 or worse elevation in lipase, and 10 (8%) of patients had grade 3 or worse elevations of both enzymes.32 There were only two cases of acute pancreatitis. Elevations in pancreatic enzymes may not be because of underlying pancreatic inflammation, but they may be because of T cell–mediated inflammation of other organs that produce these enzymes. Other nonimmune-mediated causes for pancreatic enzyme elevation should also be considered, such as pancreatic duct obstruction from metastatic disease and renal failure (which can delay clearance of these enzymes).33

Immunosuppression with corticosteroids should be reserved for patients with pancreatitis because of checkpoint inhibitors. The diagnosis of acute pancreatitis should be suspected in a patient with acute onset of a persistent, severe epigastric pain. The diagnosis of acute pancreatitis requires the presence of two of the following three criteria: acute onset of persistent, severe epigastric pain often radiating to the back, elevation in serum lipase/amylase to three times or higher the upper limit of normal, and characteristic findings of acute pancreatitis on abdominal imaging.

The significance of checkpoint inhibitor–associated pancreatic enzyme elevations in patients without acute pancreatitis is unclear. Although subclinical pancreatic inflammation has been associated with pancreatic exocrine insufficiency and diabetes, the risk of these in patients with asymptomatic pancreatic enzyme elevations is unclear. Routine assessment of these enzymes in asymptomatic patients should not be performed unless warranted by trial protocol.34 Patients with pancreatic enzyme elevations without abdominal pain or evidence of acute pancreatitis on abdominal imaging (contrast enhanced abdominal CT scan or MRI) can be monitored clinically without the need for immunosuppressive therapy. In patients with pancreatic enzyme elevations while on a checkpoint inhibitor, data on the likelihood of such a reaction recurring (or acute pancreatitis) with an alternative checkpoint inhibitor are lacking.

CONCLUSION

In summary, inhibition of immune checkpoints has improved outcomes in patients with several different types of cancer. Immune-related gastrointestinal and hepatic effects of anti–PD-1/PD-L1 monoclonal antibodies seem to be less
severe compared with ipilimumab, but the incidence with combinations of immune checkpoint–blocking antibodies is higher than with either single agent. New insights into our understanding of these toxicities may lead to the development of novel treatment strategies. However, early recognition of these toxicities and collaborative multidisciplinary care are crucial in minimizing the impact of these complications on planned antineoplastic therapy.

References


Cancer of unknown primary site (CUP) is a clinical syndrome that includes many different cancer types and accounts for approximately 2% of all cancer diagnoses. Although the anatomic primary sites in patients with CUP cannot be identified clinically, they are identified in approximately 75% of postmortem examinations, and most are less than 1 cm in size.1,2 The biologic mechanisms underlying this unique clinical behavior (i.e., dissemination of cancer while the primary site remains small) is unknown; to date, no specific molecular signatures have been associated with these cancers.

Patients should be diagnosed with CUP only after specific clinical and pathologic studies have been completed.3 Clinical evaluation includes complete history and physical examination, complete blood counts, serum chemistries, urinalysis, CT scans of the chest/abdomen/pelvis, mammogram (women), and serum prostate-specific antigen (men). Pathologic evaluation includes histologic examination and selected immunohistochemical (IHC) stains. When these evaluations are used to define CUP, detection of an anatomic primary site at any time during the subsequent clinical course is uncommon (< 10%).

Treatment of patients with CUP initially is dependent on identification of favorable subsets of patients with specific clinical and/or pathologic presentations.3 These patients (15% to 20% of all patients with CUP) respond relatively well to specific therapies, and some have potentially curable cancers. The remaining 80% to 85% of patients with CUP have traditionally received empiric chemotherapy with regimens designed to have some efficacy in a broad spectrum of cancer types (e.g., taxane/platinum, gemcitabine/platinum).3,6

As treatment improves and becomes more type-specific for many advanced cancers, the notion that empiric chemotherapy can provide adequate therapy to a heterogeneous population of patients with many different cancer types becomes increasingly outdated. Non–small cell lung cancer (NSCLC) and colorectal cancer, both common postmortem diagnoses in CUP series, illustrate the problems involved in empiric treatment. Fifteen years ago, treatment of advanced NSCLC with paclitaxel/platinum (a commonly used empiric CUP regimen) would have provided reasonable treatment. Today, 13 additional drugs are approved for treatment of NSCLC, none of which is approved (or routinely used) in the empiric treatment of CUP. In the treatment of advanced colorectal cancer, even first-line empiric CUP regimens, such as taxane/platinum, are not optimal, and none of the 10 other drugs approved for this indication is used.

The era of precision medicine in oncology offers promise for improved diagnosis and better therapy for patients with the CUP syndrome, and first steps have already been taken toward incorporating precision medicine into the routine management of disease in these patients. This brief review examines new diagnostic methods available for detection of the specific cancer type in these patients. Next, precision treatment for patients with CUP, guided by molecular identification of the cancer type and the detection of actionable molecular alterations, is discussed.

**DIAGNOSIS OF CUP IN THE ERA OF PRECISION MEDICINE**

The initial evaluation of CUP has always been predicated on the assumption that identification of a primary site or specific cancer type can improve the efficacy of treatment. The questions underlying this assumption have been difficult to address: (1) Do patients with unknown primary site actually have a primary site? The fact that most patients have small primary sites found at autopsy provides strong affirmative evidence. (2) Do CUPs mirror their counterparts that present with overt primary sites in most aspects of tumor biology, even though they differ in the ability to metastasize widely (mechanism unknown) while the primary tumor remains small? (3) Do CUPs respond to the same treatments proven effective in patients with the corresponding cancers of known primary site? Until recently, testing of the second and third questions was indirect, because most patients with
CUP never have anatomic primary sites identified. During the past 10 years, improved diagnosis has provided much more information with which to address these questions.

**IHC Staining**

IHC staining has been part of the standard pathologic evaluation in CUP for the past 20 years. During that time, stains of increased specificity have been developed. Although standard practice varies, most pathologists use panels of IHC stains to narrow the diagnostic spectrum; use of additional stains is guided by the histology, clinical presentation, and results of the initial IHC panel.7

With current IHC staining approaches, a single diagnosis is predicted in 30% to 40% of patients with CUP.8-10 However, there has been reluctance to use IHC diagnoses as a guide for treatment, because the pathology report usually is somewhat equivocal and uses words and phrases like “favor” or “consistent with” rather than giving a firm diagnosis. Until recently, there has been no other method with which to test the reliability of the IHC results.

**Gene Expression Profiling**

Specific gene expression profiles are now recognized in most cancers according to their site of origin, which reflects the different expression profiles present in their normal tissues of origin.11 The application of these findings to cancer diagnosis was first demonstrated when differences in gene expression allowed the distinction of acute myeloid leukemia from acute lymphoblastic leukemia.12 Differences in gene expression also allow distinction between various solid tumors and provide a valuable method for diagnosis of the tissue of origin in patients with CUP. It is important to recognize that this molecular analysis, which detects patterns of gene expression unique to the tissue of origin, is different from molecular mutation profiling (discussed in the next section), which is designed to detect oncogenes and other actionable molecular alterations but which only rarely determines the cancer type.

Gene expression profiling assays with either reverse-transcriptase polymerase chain reaction or gene microarray techniques are now commercially available. These assays, termed molecular cancer classifier assays (MCCAs), are able to identify more than 40 different cancers and cancer subtypes. In validation studies in cancers of known primary sites (biopsies from primary and metastatic sites), these assays correctly identified the tumor type in more than 85% of cases.11,13 In a group of 252 patients with CUP whose diseases were studied prospectively, primary sites were predicted in 247 (98%) by using the 92-gene CancerTYPE ID assay; only five patients had unclassifiable gene expression profiles.13 As with IHC, the accuracy of these diagnoses is difficult to establish, because anatomic primary sites usually are not identified. However, in a group of 24 patients with CUP who had a primary site identified 2 to 79 months after an initial diagnosis, the correct primary site was predicted by MCCA in 18 (75%) of 24 patients who had adequate tissue available for analysis.14,15

The accuracy of IHC staining compared with MCCA diagnoses has been studied in several trials. In two trials, pathologists were blinded to the tumor type and performed IHC stains (as many as they thought necessary) compared with MCCA in patients with metastatic carcinoma of known primary.9,16 In both studies, the MCCA was more accurate; differences were accentuated when tumors that were poorly differentiated (83% vs. 67% accurate in poorly differentiated carcinomas).16 In patients with CUP, the predictive accuracy of IHC (i.e., prediction of a single site of origin) decreases to 30% to 40%.8,10 In the largest study of 149 patients with CUP, IHC results performed at the time of initial evaluation were compared with MCCA results obtained later with remaining tumor tissue.8 IHC evaluation resulted in the prediction of a single site of origin in 35%. In these patients, MCCA results matched the IHC results in 77% of patients. MCCA predicted the primary site in most of the remaining 65% of patients when IHC gave nonspecific results.

Gene expression profiling also results in a high percentage of diagnoses in the uncommon group of patients with poorly differentiated neoplasm of unknown origin. In a group of 30 such patients without a lineage diagnosis after complete pathologic evaluation (median, 18 IHC stains performed), MCCA established the tumor lineage in 25 (83%) of 30 patients and a specific diagnosis in the 10 patients with carcinomas.17 Results with MCCA provide strong evidence that most CUPs retain gene expression profiles similar to their tissue of origin and suggest that responses to site-specific treatment may also mirror their counterparts with known primary site.

**TREATMENT OF CUP IN THE ERA OF PRECISION MEDICINE**

For the majority of patients with CUP, empiric combination chemotherapy traditionally has been considered the standard first-line therapy. Benefits of this approach are modest: standard regimens produce response rates less than 40%, median survival of fewer than 11 months, and 2-year survival less than 20%.4,6 Because the site of origin can be determined now in most patients with CUP, site-specific treatments that are based on these molecular diagnoses have been investigated for several years, and these data are reviewed.

For many advanced cancer types, standard treatment now includes the identification of patient subsets defined by the presence of actionable molecular alterations (e.g., HER2 in breast cancer; EGFR/ALK/ROS1 in NSCLC). Analogous molecular testing and targeted treatment of patients with CUP whose cancer types have been diagnosed should also be considered; data to support this approach are developing. Beyond testing for specific molecular alterations that are based on the cancer type, increasing evidence indicates that comprehensive genetic profiling of tumors can identify additional targetable molecular alterations in substantial numbers of patients with advanced cancer. Although evidence in patients with CUP is still limited, these issues are also discussed.
Site-Specific Therapy by Molecular Cancer Classifier Assay Diagnosis

Evidence supporting the use of site-specific therapy directed by the MCCA results is incomplete but is increasingly compelling. Although results of a randomized comparison of site-specific therapy and empiric chemotherapy has not been reported, the available data strongly suggest that outcomes are improved with site-specific therapy, particularly for the more responsive cancers.18-20

The largest prospective trial to date included 194 previously untreated patients with CUP who received site-specific therapy on the basis of a MCCA diagnosis.18 The median survival of all patients was 12.5 months; patients predicted to have responsive tumor types had significantly longer median survival than those with less responsive types (13.4 vs. 7.6 months). Although patient numbers in specific tumor groups were relatively small, survival generally mirrored the expected survival of patients with the predicted cancer types (biliary, 7 months; pancreas, 8 months; colon, 13 months; ovarian, 30 months; and breast, not reached at > 24 months).

Other recent studies also support the use of site-specific treatment on the basis of MCCA results. In one study, a MCCA resulted in a diagnosis in 188 (87%) of 216 patients with CUP.18 Treatment received by 114 patients was examined retrospectively: patients who received treatment predicted effective for their MCCA diagnosis had median survival of 13.6 months compared with a 6-month median survival for those who received empiric treatments predicted ineffective. Another trial used an empiric regimen of carboplatin/paclitaxel/everolimus; the 18 patients predicted by MCCA to have tumor types sensitive to this regimen had a median survival of 17.8 months, but the 19 patients with tumor types predicted to be insensitive had a median survival of 8.3 months.20

Additional retrospective studies focusing on specific tumor types also support this approach. In three studies, patients with CUP who were predicted to have metastatic colorectal cancer (all had negative colonoscopies) had median survivals of more than 20 months when treated with colorectal cancer therapies.21-23 In a group of 20 patients predicted to have renal cell carcinoma (none had renal lesions on CT scan), site-specific treatment with targeted agents resulted in a median survival of 16 months.3,24 Patients predicted to have germ cell tumor, lymphoma, and neuroendocrine tumors have had typical responses to site-specific therapy for these tumor types.3,17

When patients with CUP are treated with site-specific treatment, it is reasonable to test a tumor biopsy specimen for specific molecular alterations on the basis of the predicted site of origin by using either specific hotspot genetic testing or comprehensive molecular profiling. Examples include testing for HER2 after the diagnosis of breast/gastroesophageal junction/gastric cancer; testing for EGFR/ALK/ROS1 after the diagnosis of NSCLC, and testing for KRAS/microsatellite instability (MSI) after the diagnosis of colorectal cancer. At present, only anecdotal reports document responses to targeted treatment in these patients (e.g., NSCLC with EGFR mutation responding to gefitinib; NSCLC with ALK rearrangement or MET amplification responding to crizotinib; HER2-positive breast cancer responding to trastuzumab).18,25-30 Additional studies in this area are needed.

The rapid development of checkpoint inhibitors and other immunomodulatory agents creates additional possibilities for treatment in patients with CUP. At present, there are only a few case reports about these treatments.31,32 Studies in patients with CUP who are predicted to have potentially sensitive tumor types (e.g., lung, urothelial, renal) are indicated.

Comprehensive Molecular Profiling in CUP

The role of comprehensive molecular profiling is evolving rapidly. Already, the increased use of comprehensive profiling has enabled the testing of targeted agents in a wide variety of advanced cancer types that are rare or have a low incidence of the critical mutations. Not surprisingly, effective targeted agents have activity across a spectrum of tumor types, as long as the critical molecular alteration is present.33-36 For example, HER2 amplification/overexpression predicts response to HER2-targeted therapy in colorectal carcinomas, salivary gland carcinomas, and others, in addition to the cancer types for which HER2-targeted therapy is currently labeled.33 Presence of the BRAF V600E mutation predicts response to BRAF-targeted drugs in NSCLC, ovarian cancer, and others.33,35

The efficacy of targeted agents varies widely on the basis of solid tumor type. The most dramatic example of this is the high response rate of metastatic BRAF V600E–mutated melanoma (> 60%) when treated with BRAF inhibitors,37 and the inactivity of the same agents in BRAF V600E–mutated colorectal cancer.38 Therefore, it is unlikely that most of the current targeted agents will ever be recommended for use agnostic of tumor type. However, the U.S. Food and Drug Administration recently approved the first treatment on the basis of molecular testing alone: pembrolizumab for patients with MSI unstable tumors regardless of the cancer type.39 A new targeted drug, larotrectinib (a pan-TRK inhibitor), is likely to become the second such drug when it gains approval for patients with the uncommon TRK mutation.40

Comprehensive molecular profiling of patients with CUP indicates that a substantial number of potentially important molecular alterations are present. In a group of 200 patients with CUPs (125 with adenocarcinoma, 75 with carcinoma), potentially actionable mutations were identified in 169 (85%).34 Some of these tumors had mutations for which only investigational drugs (with undefined activity) are available, and some had mutations that may affect treatment decisions but for which no specific treatment is available (e.g., KRAS). However, 38 (18%) of 200 tumors had molecular alterations for which approved targeted agents are currently available (HER2, BRAF, EGFR, ALK, RET, BRCA, and ROS1).

Recently, ctDNA has been evaluated in 442 patients with CUP; previously characterized molecular alterations were identified in 66% of tumor specimens.31 The actionable...
mutations identified were similar to those previously reported from tests of CUP tumor tissue. Additional validation of the role of ctDNA testing is required, but such testing may have advantages compared with tissue testing.

As biomarkers predictive of response to immune checkpoint inhibitors are identified, it appears that the use of these agents in CUP holds promise, particularly because many of the cancer types identified in the CUP population are responsive to these drugs. IHC staining for PD-L1 has been of some value, but it is not strongly predictive. In a group of 70 patients with CUPs, 63% had IHC staining for PD-1 in tumor-infiltrating lymphocytes, and 21% had cancer cell staining for PD-L1. MSI and mismatch repair deficiency are associated with high response rates to checkpoint inhibitors in colorectal cancer and other tumors; pembrolizumab is now approved for advanced cancers with high MSI. The frequency of MSI and mismatch repair deficiency in CUP has not been well studied. High tumor mutation burden also has been associated with higher response rates to checkpoint inhibitors. Compared with other tumor types, high tumor mutation burden (≥ 20 mutations/mb) appears to be frequent in CUP, and the incidence varies with histology: adenocarcinoma, 8%; carcinoma, 11%; and squamous carcinoma, 23%.

The use of comprehensive molecular profiling to identify and direct therapy for CUP therefore has the potential to contribute substantially to the management of disease in these patients. At present, successful targeted treatment that is based on findings at molecular profiling has been described in anecdotal reports, but no reported prospective clinical trial has evaluated this approach. Therefore, off-study use of targeted treatment presents reimbursement challenges. Until more data exist, results from an MCCA may be helpful; for example, a patient with CUP who has an EGFR mutation and a cancer type identified as NSCLC by MCCA likely will have insurance coverage for therapy with EGFR inhibitors.

A multinational randomized study is needed to address the role of comprehensive molecular profiling in directing treatment of patients with CUP. The ongoing National Cancer Institute MATCH study and the ASCO TAPUR study will provide some additional information in patients with many advanced cancer types.

INTEGRATED APPROACH TO DIAGNOSIS AND MANAGEMENT OF CUP

A new approach to the diagnosis and management of the patient with CUP is shown in Fig. 1. Because diagnosis of the site of origin is now possible in most patients with CUP, initial evaluation closely parallels the strategy used in the initial evaluation of patients with metastatic cancer of known type (Fig. 1). In both groups, the goal of the initial evaluation is to determine optimal site-specific first-line treatment after fully characterizing the tumor type and evaluating for specific molecular subsets. For many patients with CUP, site-specific therapy differs markedly from empiric CUP chemotherapy; differences include selection of first-line chemotherapy regimens, use of targeted therapy for identified actionable mutations, and therapy of proven efficacy beyond first-line use.

The role of comprehensive molecular profiling in the management of CUP is certain to increase in the future. Although

FIGURE 1. Management of Disease in Patients With Metastatic Cancer

Anatomic primary site detected (97-98% of all patients)

Anatomic primary site not detected – CUP syndrome (2-3% of all patients)

Biopsy of appropriate lesion for histologic diagnosis

Biopsy of appropriate lesion for histologic diagnosis

Additional testing if necessary for the specific cancer type (may include tumor markers, molecular testing of biopsy)

Additional studies including selected IHC stains and MCCA if necessary

Diagnosis of single cancer type (90-95% of patients)

Empiric chemotherapy or clinical trial

Specific cancer type not diagnosed / unknown (5-10% of patients)

Continue site-specific therapy second-line and beyond if needed (may include chemotherapy, targeted drugs, immune checkpoint inhibitors, clinical trials)

Abbreviations: CUP, cancer of unknown primary site; IHC, immunohistochemistry; MCCA, molecular cancer classifier assay.
therapeutic data are still limited in CUP, identification of a molecular abnormality known to be targetable across multiple tumor types (e.g., HER2, BRAF, EGFR, high MSI, high tumor mutation burden) should lead to strong consideration of treatment with an appropriate targeted therapy, either as first-line (when other options appear unlikely to be beneficial) or subsequent treatment. However, recent suggestions that optimum therapy for CUP can be administered using only the results of comprehensive molecular profiling (i.e., knowledge of the primary site is irrelevant) are premature. At present, few targeted drugs are recommended for first-line single-agent treatment in any solid tumor type. Combination chemotherapy still plays an important role in the treatment of many cancers; few oncologists would recommend the same chemotherapy for patients with breast compared with colon cancer, nor would they treat the large majority of patients with either of these cancer types with first-line single-agent targeted therapy. Likewise, treatment of a patient with BRAF V600E–mutated cancer with current BRAF-targeted agents would be inappropriate if the primary site was known to be colorectal.

In the past, the heterogeneity of patients with CUP (including different clinical features and diverse cancer types) was an impediment to performing clinical trials and developing effective treatment. The approaches to cancer therapy are now focused on molecular cancer mechanisms, so the heterogeneity of CUPs likely will provide greater opportunities to identify treatable subsets. Additional experience with comprehensive molecular profiling, targeted treatment, and immunotherapy is essential in this patient population.

References


POINTS OF VIEW

The section contains articles describing emerging, highly debated, or controversial topics in cancer research, treatment, and care to benefit patients and the field of oncology.

ARTICLES

So Much Data, So Little Knowledge: Using Formal Logic to Aggregate Data and Interpret Information
J. Russell Hoverman
We, as human beings, have limited access to the enormous data feed to which we are exposed every day. We do not see the full spectrum of wave energy, we do not perceive the full audio range, and one only has to walk with one’s dog to realize how limited our olfactory senses are. Even the data we could theoretically perceive are too much for us. We cannot devote attention to every ray of light that hits our retina or every sound that reaches our ears. From an evolutionary perspective, we could not survive with constant data overload. We therefore filter and abstract. There are physiologic filters to much that we perceive, and the brain does the rest. Imagine an impala in the Lowveld of Southern Africa. Because impalas are under constant pressure from predators, they do not wait until they see a full-sized lion before they run. How much is enough—movement in the grass, a warning baboon call, a flash of brown? There is a fine balance between being eaten and being exhausted. In evolutionary terms, the only meaningful outcome is survival, but for our purposes, we can use outcomes (O) as a surrogate for survival in applying logic to our current use of data.

Formal logic is the use of symbols to structure how we make inferences such that the structure can be applied beyond specific cases. The structure of clinical trials and the values equation (value = outcomes/cost) lend themselves to evaluation using formal logic. Doing this demonstrates the unique position of randomized clinical trials as a defensible format for gathering information and identifies the shortcomings of historical controls and meta-analyses and retrospective studies using large databases. A practical example using literature on maintenance therapy in metastatic colorectal cancer is assessed. It is important to emphasize that value will be relative to a viewpoint, with many interested parties having competing values. This underscores the place of physicians and professional societies as putting patient values first.

Formal logic is the use of symbols to structure how we make inferences such that the structure can be applied beyond specific cases. First think of how we aggregate data. We tend to think of entities, things in our environment. For example, for another human, we group a set of data points, or characteristics to identify an individual. We can organize that into a formula for that individual as follows: \( I(a_1 + a_2 + a_3 + a_4 + \ldots a_n) \), where ”I” is an individual with the characteristics \( a_1 \) to \( a_n \) and \( x \) is the number of those individuals with those characteristics. By this process, we have progressed from raw data to information about our environment.

We can step back now and see where “data” become “knowledge.” The discrete characteristics are data points, but when put together they apply to individuals and become information. They define entities in our environment. We then take these entities and put them in situations where we can learn about them, about an intervention, or an action for which we will change our own behavior. It is only when we apply a structure to both data and information to produce an actionable result that we have knowledge.

In the data storm we now confront, these same principles pertain. We want to interrogate data for a reason. In cancer care, it may in fact be survival, but it may also be some aspect of life of concern for us. We search for something that is beneficial for us or some one of us. The value equation denotes nicely how we can think of this. In this case, value = outcome/cost. This is the inverse of the risk/reward calculation. Most important, it is a value for someone, directly or indirectly. When we provide services, we may benefit any number of entities—patients primarily, but also the physician and staff, health care entities such as hospitals, imaging centers, laboratories, and even society. Any of these entities may have competing values and these competing values have to be judged relative to the values of others. Even a single patient may have competing values, such as a particular toxicity versus response rate or child care or work attendance versus treatment schedule. These become relative.
values (RVs) that are incorporated into the decision process. In its simplest structure, for our patients with cancer, value will be tied to survival; but even for individuals, there will be RVs, the importance of which can only be assessed by our patients.

We can now go back to logical structures to format how we examine data to address value and RV. The first step is to format historical controls. The logical structure looks as follows: here the intervention is “b” and b is tested compared with an historical population; however, there is no guarantee that the historical population is identical for relevant characteristics and logically, comparisons are not possible.

Historical Control

\[
q \{I (a_1 + a_2 + a_3 \ldots a_n) + b\} \rightarrow O_1
\]

\[
r \{I (a_1 + a_2 + a_3 \ldots a_n) + b\} \rightarrow O_2
\]

The second format is a process improvement structure. This looks like a transformational structure in which many changes are made at one time.

Process Improvement

\[
n \{I (a_1 + a_2 + a_3 \ldots a_n + b + c + d)\} \rightarrow O_1
\]

\[
m \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_2
\]

Transformational or project improvement projects may have only historical controls and the experimental group may have an “n” of only 1. If there is change, the study owners will be unable to identify the critical contribution of each component to value. For cancer care, the current blue whale of process improvement projects is the oncology care model, with six major requirements, 10 characteristics of navigation, 13 components of the treatment plan, and numerous quality metrics. The number of variables can be daunting and controlling for those variables can be challenging.

PRACTICAL APPLICATIONS

- Formal logic can help interpret oncology trials and literature.
- Randomized controlled trials have the most logically structured format.
- The use of formal logic allows us to better understand the value of treatments in trials.
- Value always has an interested party, and often there are multiple parties with competing interests.
- It is the role of physicians and professional societies to place patient values first.

In addition to these simple equations, there is a structure for meta-analysis as follows:

Meta-analysis or Retrospective Studies of Large Databases

\[
q \{I (a_1 + a_2 + a_3 \ldots a_n) + b\} \rightarrow O_1
\]

\[
r \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_2
\]

\[
r \{I (a_1 + a_2 + a_3 \ldots a_n + b)\} \rightarrow O_3
\]

\[
s \{I (a_1 + a_2 + a_3 \ldots a_n + b)\} \rightarrow O_4
\]

\[
t \{I (a_1 + a_2 + a_3 \ldots a_n + b)\} \rightarrow O_5
\]

\[
t \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_6
\]

\[
q \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_7
\]

\[
r \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_8
\]

In this format, “q,” “r,” “s,” and “t” ideally represent separate randomized controlled trials but may include single-arm trials with historical controls. By combining studies, large numbers may enhance the conclusions. From a logical standpoint, because the populations are different, no amount of statistical manipulation can guarantee, based on structure alone, that any conclusion can isolate the experimental variable. The same can be said for large database studies. The number of variables can be daunting and controlling for those variables can be challenging.

One can argue that these challenges can be overcome by single patient meta-analyses or our current sophistication with interrogating large databases. We can be hopeful about this. But, in addition to location, treatment sites, physician training, socioeconomic status, geographic and ethnic variation, age, and comorbidity, among many others, time itself is a variable. The simplest and most reliable format is the randomized controlled trial (RCT). The reliability of conclusions from these large databases will depend on its approximation to the RCT structure.

The logical structure of the RCT may have three versions, all of which share the characteristic of examining only one variable. In RCT 1, the populations are identical and only one intervention is made. In RCT 2, the placebo effect (p) of the treatment arm is accounted for in the control arm. In RCT 3, the comparison is between a new treatment or intervention (b) and the standard of care (d).

RCT 1

\[
q \{I (a_1 + a_2 + a_3 \ldots a_n) + b\} \rightarrow O_1
\]

\[
q \{I (a_1 + a_2 + a_3 \ldots a_n)\} \rightarrow O_2
\]
The RCT is, of course, not without its problems. Logically, only one variable is tested and we can make conclusions about comparative outcomes. In real life, we cannot guarantee that both arms are equal and that results did not occur as part of the random variation of events. The result, for example, improved survival measured by \( O_1 \) to \( O_2 \) is dependent on the probability relationship between the two outcomes. There are other concerns, such as selection bias, reporting bias, more than one variable treated as one (intervention plus maintenance therapy, for example), selection of outcomes (response rate vs. progression-free survival [PFS] vs. overall survival [OS]), and lack of cost data. In regard to cost (C), the ideal format for presentation to our patients is in terms of RV, with a structure as follows:

\[
RV_1 = \frac{O_1}{C_1} \\
RV_2 = \frac{O_2}{C_2} \\
RV_3 = \frac{O_3}{C_3}
\]

Ultimately, the choice of the many options for lung cancer, prostate cancer, or breast cancer will depend on the subjective values of our patients. This may include dollar cost, time cost, toxicity cost, or even the cost of not dying at home or placing undue burden on family and friends. We cannot know these things until we ask and we cannot give our best answer until we have better knowledge.

The interpretation of cancer treatment literature can be daunting but the use of formal logic can provide some clarity. One example formats the use of maintenance chemotherapy after first-line chemotherapy in adjuvant metastatic colorectal cancer. The studies can be simplified by making some structural assumptions as follows. First, assume all studies have the same population. Second, the formulas assume that all populations have the structure \( x(\{a_1 + a_2 + a_3 \ldots + a_n\}) \). Finally, the following designate general categories of regimens without attention to dosing or schedule: 5-flourouracil (5-FU)/leucovorin/oxaliplatin (FOLFOX) with or without bevacizumab (BEV), 5-FU/leucovorin/irinotecan (FOLFIRI) with or without BEV, capecitabine/oxaliplatin (XELOX) with or without BEV, and maintenance fluoropyrimidine (MFP; which could be either 5-FU or capecitabine) with or without BEV. The relevant studies look as follows:

**OPTIMOX2**

\[
\text{FOLFOX + BEV} \rightarrow O_1 \\
\text{FOLFOX + BEV + MFP (infusional 5-FU)} \rightarrow O_2
\]

Result: \( O_2 > O_1 \). Small improvement in PFS, no OS difference

**AIO0207**

\[
\text{FOLFOX + BEV + (MFP + BEV)} \rightarrow O_1 \\
\text{FOLFOX + BEV + maintenance BEV} \rightarrow O_2 \\
\text{FOLFOX + BEV + observation} \rightarrow O_3
\]

Result: \( O_1 > O_3 \). No superiority or noninferiority of \( O_2 \) to either \( O_1 \) or \( O_3 \)

Luo et al

\[
\text{FOLFOX + MFP (capecitabine)} \rightarrow O_1 \\
\text{FOLFOX + observation} \rightarrow O_2
\]

Result: \( O_1 > O_2 \). Improved PFS, no OS difference.

**CAIRO3**

\[
\text{XELOX + BEV + MFP (capecitabine) + BEV} \rightarrow O_1 \\
\text{XELOX + observation} \rightarrow O_2
\]

Result: \( O_1 > O_2 \). Improved PFS, no improvement in OS.

In summary, no study shows that BEV adds anything to an MFP regimen. The CAIRO3 study had no capecitabine-only maintenance arm. The AIO0207 study had no 5-FU-only maintenance arm. In the latter study, there was no evidence that BEV alone was better than the observation arm. It is no surprise that a recent study with the following structure shows no benefit to BEV maintenance.

**PRODIGE9**

\[
\text{FOLFIRI + BEV + BEV maintenance} \rightarrow O_1 \\
\text{FOLFIRI + BEV + observation} \rightarrow O_2
\]

Result: \( O_1 = O_2 \). No improvement in PFS or OS.
This is important because the differences in value can be profound among these regimens. For discussion, suppose BEV is 25 times the cost of 5-FU regimens for maintenance. Taken another way, the margin of 6% on a $100 drug will be $6, and a 20% margin will be $20. The margin of 6% on a $2,500 drug will be $150, and a 20% margin will be $500. Because there were no differences in outcomes with adding BEV, any BEV regimen for maintenance is of low value compared with fluoropyrimidine regimens.

These conclusions lead to the last point to make. All RVs are laden with moral tension. The outcomes and costs apply to someone or something. A RV released into the world will be assessed by entities with competing interests. A new treatment, for example, will interest patients, physician groups, hospitals, insurers, pharmaceutical companies, and even Wall Street. The perception of RV will be different for each. What is best for one may not be best for patients unless the values for each are tied to patient values. These competing interests may lead to distortion of the RV calculations. The unique role of physicians and professional societies is their allegiance to patient values.

References

BREAST CANCER
Advances in Fertility Preservation for Young Women With Cancer
Karen Lisa Smith, MD, MPH, Clarisa Gracia, MD, MSCE, Anna Sokalska, MD, PhD, and Halle Moore, MD

OVERVIEW

Female patients of reproductive age with cancer often require treatment that can compromise their future fertility. Treatment-related infertility is an important cancer survivorship issue and is associated with depression and diminished quality of life. Recent advances in reproductive health care provide the opportunity to preserve fertility prior to the initiation of cancer therapy. Clinical guidelines recommend that oncology providers counsel patients about the risk of treatment-related infertility and fertility preservation options, and that they refer those who are interested in fertility preservation to fertility specialists. Guidelines endorse the use of assisted reproductive techniques (ART) provided by reproductive endocrinologists to preserve fertility in young female patients with cancer. In addition, ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists may be considered for ovarian protection during chemotherapy. This article reviews currently available and emerging ART for fertility preservation in female patients of reproductive age with cancer and current data supporting the use of ovarian suppression for ovarian protection during chemotherapy in this population. We also review the uptake of fertility services and discuss barriers to fertility preservation in female patients of reproductive age with cancer.

Each year, over 30,000 women of reproductive age are diagnosed with cancer in the United States. Common cancers in young women include breast cancer, hematologic malignancies, gynecologic malignancies, sarcomas, brain tumors, and colorectal cancer. Given the current trend toward delayed childbearing in Western countries, many young women with cancer have not yet completed their families at the time of diagnosis.

Unfortunately, young women with cancer often require treatment that can compromise future fertility. Chemotherapy is toxic to the ovaries and can result in loss of primordial follicle reserve and premature ovarian failure. The degree of gonadotoxicity associated with each chemotherapy regimen varies according to the drug class(es), duration/dose of chemotherapy, and patient age. DNA damage induced by alkylating agents results in primordial cell death in the ovary, leading to a particularly high risk of subsequent infertility. Chemotherapy accelerates the natural age-related decline in follicle reserve, thus the likelihood of treatment-related infertility is greater in women who receive chemotherapy later in their reproductive years. In the case of hormone receptor–positive breast cancer, additional risk of infertility beyond that induced by chemotherapy occurs due to the need to delay conception during the course of 5 to 10 years of adjuvant endocrine therapy. Additionally, in some situations, future fertility may be impacted by the direct effects on the reproductive organs of radiation and/or surgery in the abdomen or pelvis, although fertility-sparing procedures can be considered if appropriate. The impact of newer targeted therapies on female fertility is not well defined. Data suggest that trastuzumab does not increase the risk of infertility in female patients with breast cancer, and pregnancies have been reported in patients treated with imatinib; however, conception should be avoided during the course of targeted therapies.

With recent improvements in cancer survival rates, long-term effects of cancer treatment, such as infertility, have become important clinical issues. The majority of young female cancer survivors report reproductive concerns and many desire children. To date, available data indicate that pregnancy after cancer treatment does not increase the risk of cancer recurrence, even in women with a history of hormone receptor–positive breast cancer. Yet, female cancer survivors achieve pregnancy at lower rates than unaffected women in the general population.

Recent advances in reproductive health care provide the opportunity to preserve fertility in female patients prior to the initiation of cancer therapy. Guidelines recommend that oncology providers counsel patients about the risk of treatment-related infertility and fertility preservation interventions, and that they refer those who are interested in fertility preservation to fertility specialists. If considered
safe from an oncologic perspective, fertility concerns should be addressed as soon as possible after a cancer diagnosis and prior to the initiation of cancer therapy.21,23,27

Despite clinical guidelines outlining optimal management of fertility issues in the setting of a cancer diagnosis, many patients with cancer do not recall discussing their risk of infertility and fertility preservation options with their oncology providers.13,15,28,29 Overall, data suggest that patients desire more information about fertility issues and that a substantial proportion feel their fertility concerns are not adequately addressed by their oncology care teams.13,15,17,29-35 Concerns about fertility impact cancer treatment decisions in approximately one-fourth of young female patients with breast cancer, emphasizing the importance of addressing the risk of infertility and fertility preservation options in order not to compromise delivery of optimal cancer therapy.13,15 In addition, reproductive concerns in female cancer survivors are associated with lower quality of life, increased distress, and increased depression, again highlighting the importance of addressing fertility issues with patients.16,35-38

Guidelines support the use of ART offered by reproductive endocrinologists to preserve fertility in female patients with cancer of reproductive age.21-27 In addition, ovarian suppression during chemotherapy can be considered as an approach for preserving fertility and preventing early menopause, although data are conflicting.25-27,39 Fertility preservation prior to cancer therapy is safe and can often be accomplished without significant delay in cancer care, especially if patients are referred early in the course of their cancer treatment planning.40,41 This article reviews current and emerging options for fertility preservation in female patients of reproductive age with cancer. We also review uptake of fertility services and barriers to fertility preservation in this population.

ASSISTED REPRODUCTIVE TECHNIQUES

The rapid development of ART over recent years has brought a wide range of fertility preservation options to young women diagnosed with cancer. An overview of currently available established and investigational ART for fertility preservation is presented in Figure 1.

Embryo cryopreservation (Fig. 1, Box 1) is an established method of fertility preservation that can be offered to postpubertal women who have a committed partner or who are willing to use donor sperm. To date, data on success rates based on the number and quality of cryopreserved embryos in patients with cancer are limited, however, they appear to be similar to those in the general population of couples with infertility. For example, in vitro fertilization (IVF) registry data from the Society of Assisted Reproductive Technology derived primarily from infertile couples (www.sartcorsonline.com) indicate that transfers of cryopreserved embryos lead to live birth rates that are at least as good as fresh embryo transfers, and that the live birth rate per frozen embryo transfer is 43% in women younger than age 35. Pregnancy and live birth rates decline as women age. Similarly, among 131 patients with breast cancer who underwent embryo cryopreservation prior to breast cancer systemic therapy, 33 patients returned a median of 5.25 years later for autologous frozen embryo transfer or used a gestational carrier. The rate of live birth per frozen embryo transfer was 45%.42

Mature oocyte cryopreservation (Fig. 1, Box 2) is now considered a standard-of-care approach to fertility preservation and can be offered to postpubertal patients who do not have a partner or to those with a partner who do not wish to cryopreserve embryos.43 It is important to recognize the pivotal role of vitrification (a method of cryopreservation using high initial concentrations of cryoprotectant and ultra-rapid cooling to solidify the cell into a glass-like state without the formation of ice) compared with slow freeze for improving oocyte cryopreservation success.46 Overall, as reported by Cobo et al, the live birth rate per oocyte thawed is 6.5% and the cumulative live birth rates increase with the number of oocytes cryopreserved.44 Four randomized controlled trials demonstrate that implantation and clinical pregnancy rates are similar for fresh and vitrified-warmed oocytes.45-48 However, given the limited number of trials, it is unclear if these data are generalizable. Indeed, national IVF data from the Society of Assisted Reproductive Technology suggest that live birth rates per embryo transfer are lower when frozen donor eggs are used (44%) compared with fresh donor eggs (58%). To date, there are only limited data on pregnancy outcomes from frozen eggs in patients who cryopreserved oocytes before cancer therapy; however, the success rates are comparable to the general population.49

Both embryo cryopreservation and mature oocyte cryopreservation require ovarian stimulation followed by egg retrieval. The process of controlled ovarian hyperstimulation takes approximately 2 to 3 weeks and, therefore, has the potential to delay cancer therapy briefly. Controlled ovarian hyperstimulation should be performed before gonadotoxic therapy is initiated. Selecting an appropriate stimulation protocol and gonadotropin dose depends not only on a patient’s age and ovarian reserve as assessed by follicle-stimulating hormone level, anti-Mullerian hormone level,
and the antral follicle count, but also on the type of malignancy and the available time before the initiation of cancer therapy. The goal is to obtain a high number of oocytes, usually during only one cycle due to time constraints, and to minimize the risk of ovarian hyperstimulation syndrome, which can delay and complicate cancer therapy. Using a gonadotropin-releasing hormone (GnRH) antagonist protocol with a GnRH agonist to trigger final maturation of oocytes may reduce the risk of ovarian hyperstimulation syndrome.50 Initiation of the stimulation at any time of the menstrual cycle (so-called “random-start controlled ovarian stimulation”) has been shown to be effective and limits the time required for controlled ovarian hyperstimulation and egg retrieval to 2 weeks, reducing delay in cancer therapy.51-55 Adding an aromatase inhibitor to the stimulation protocol lowers the circulating estrogen levels and is often used in patients with estrogen-sensitive tumors such as breast cancer.50,56 Some studies suggest that the oocyte yield with controlled ovarian hyperstimulation may be impaired in patients with cancer even before gonadotoxic therapy, however, available data are conflicting.57-59

Initiating fertility preservation before cancer treatment may not be always feasible. Although it may be possible to stimulate the ovaries during or immediately after chemotherapy, there is concern about egg quality. To the best of our knowledge, there is no human data assessing pregnancy outcomes in this clinical scenario; however, animal data indicate that conception within 3 months of chemotherapy is associated with lower implantation rates and higher rates of resorption and malformation.60 Survivors remote from gonadotoxic therapy may have a compromised response to ovarian stimulation.61 Our group compared the response to stimulation in 35 survivors who had previously been exposed to chemotherapy to 95 patients who were newly diagnosed with cancer. As expected, anti-Mullerian hormone level and antral follicle count were impaired in the survivors, and they required a higher total dose of gonadotropins to stimulate the ovaries. One-quarter of the cycles in survivors were cancelled, and egg retrieval was not performed; however, those whose cycles were completed obtained a median of 10 eggs, which was no different from the newly diagnosed patients. However, the quality of these eggs is not known, and more data are needed to routinely recommend oocyte cryopreservation in cancer survivors after exposure to chemotherapy.62

A potential benefit of cryopreserving oocytes or embryos is that preimplantation genetic testing may be possible. After fertilization and culture, embryos can be biopsied

**FIGURE 1.** Established and Investigational Assisted Reproductive Techniques for Fertility Preservation in Females

Box number correlates with numbers in text.
Abbreviations: GV, germinal vesicle; MI, oocyte in meiosis I.
at the blastocyst stage, and several cells may be sent for genetic analysis to identify a known genetic mutation such as a *BRCA* mutation and/or to perform aneuploidy screening.63 Prematuration genetic testing may allow couples to avoid passing a known mutation to their offspring.

Although many cancer survivors may be candidates for carrying a pregnancy after treatment, some survivors will experience late effects of therapy or receive ongoing cancer therapies that make it unsafe or impossible to successfully carry a pregnancy. Cryopreserved embryos or embryos from cryopreserved oocytes may be transferred to a gestational carrier in the future if a patient is unable to carry a pregnancy herself.

Patients requiring pelvic radiation may benefit from ovarian transposition to a site outside the region of maximal radiation exposure. This procedure may be performed at the time of an oncology procedure. In these cases, transabdominal oocyte retrieval may be necessary.23

In vitro maturation of immature oocytes (Fig. 1, Box 3) is an investigational approach that has received some attention in the field, especially as an option for patients who need to initiate gonadotoxic therapy quickly and for patients with hormone-sensitive tumors.64 Several different protocols have been described for retrieving oocytes without prior stimulation, or with only minimal stimulation using a few days of follicle-stimulating hormone, priming with human chorionic gonadotropin (HCG) only or a combination of this hormone with follicle-stimulating hormone.65 Most of the data for this technique come from patients with polycystic ovarian syndrome or from patients with morphologically and endocrinologically normal ovaries rather than from patients with cancer.66,67 Potential advantages of this approach include shorter time to oocyte retrieval, lower estradiol levels, lower dose of medications, decreased risk of ovarian hyperstimulation syndrome, and reduced cost. Typically, protocols start with the onset of the menses, precluding the flexibility of a random start. Notably, data have consistently demonstrated lower implantation and pregnancy rates with this approach compared with standard IVF.68,69 To date, there is also little known about the risk of malformations and developmental outcomes in children conceived with in vitro matured oocytes.70,71 This approach remains investigational at this time.

Ovarian tissue cryopreservation (Fig. 1, Box 4) is currently considered an experimental method of fertility preservation suitable for patients who require immediate cancer therapy. Ovarian tissue cryopreservation is the only fertility preservation option for prepubertal girls.72,73 It results in a minimal delay in treatment and can even be performed after exposure to some chemotherapy. It requires removal of the entire ovary or cortical biopsies, typically with a laparoscopic procedure, followed by cryopreservation of the ovary or of small fragments of ovarian cortex. Removing ovarian tissue can be coordinated with another procedure (i.e., tumor resection, port placement, bone marrow aspiration) or as a part of a combined fertility preservation procedure (e.g., at the time of ovarian transposition in preparation for pelvic radiation or immediately after oocyte retrieval to increase the efficacy of fertility preservation).74 Despite the success of transplantation of the whole fresh ovary, no report of successful transplantation of initially cryopreserved ovary in humans is available. Heterotopic ovarian cortex transplantation to sites outside the ovary or pelvis (such as abdominal wall, rectus muscle, subperitoneal, forearm, or chest wall) followed by IVF has resulted in only one clinical pregnancy in humans to date.75 and orthotopic tissue transplantation to the ovary/pelvis appears to be the most successful approach for using the tissue. In this clinical scenario, pregnancy may be spontaneous after transplanting the ovarian tissue back to the pelvis or may be achieved using IVF. The function of the ovarian tissue typically resumes 60 to 240 days after transplantation and lasts for between several months and 7 years depending on factors such as patient age, timing of tissue cryopreservation, and amount of tissue transplanted. Given that viability of ovarian tissue transplant is limited, the procedure should be performed when the patient is ready to achieve pregnancy. Since the first pregnancy reported in 2004, there have been over 130 live births reported after ovarian tissue transplantation.73

Ovarian tissue autotransplantation carries the potential risk of reseeding with cancer cells. The magnitude of this risk is not known and differs by cancer type and the method by which the tissue is analyzed.76 For example, malignant cells have not been detected in ovarian cortical tissue obtained from patients with leukemia using immunohistochemical stains, but have been identified in 85% of samples when analyzed by quantitative reverse transcription polymerase chain reaction.77 Due to this concern, ovarian tissue autotransplantation is not recommended for women with blood-borne malignancies, ovarian cancers, malignancies that can result in metastasis to the ovary, or an inherent predisposition to ovarian cancer.72,78

Another experimental option for utilizing ovarian tissue that avoids the risk of reintroducing malignancy is isolation of immature oocytes from tissue removed during ovarian tissue–harvesting at the time of the initial surgery followed by in vitro maturation and IVF or cryopreservation (Fig. 1, Box 5).79,80 To date, one live birth in humans has been reported from this technique.81 Several new avenues of scientific investigation could have tremendous implications for fertility preservation in patients with cancer in the future. For example, there has been significant interest in developing strategies to eliminate the risk of seeding cancer cells through ovarian tissue transplantation. Several methods have been proposed such as isolating ovarian follicles from ovarian tissue followed by in vitro development of primordial follicles, or creating an artificial ovary and grafting it to the pelvis (Fig. 1, Box 6).82,83

In 2012, stem cell biologists in Japan reprogrammed mouse skin cells into primordial germ cells by combining them with embryonic or nonembryonic stem cells (Fig. 1, Box 7). These cells were then placed in the ovaries or testes of mice to mature into competent eggs and sperm. Using IVF and intracytoplasmic sperm injection, live births were
reported. In 2017, another Japanese group reconstituted the entire process of oogenesis from mouse pluripotent stem cells in vitro, leading also to live births in mice, supporting the potential of stem cells as a future direction for fertility preservation. While promising avenues for the future, the artificial ovary and the development of primordial germ cells obtained from transformed in vitro stem cells currently do not have human data available.

**OVARIAN FUNCTION SUPPRESSION**

Ovarian function suppression with GnRH agonists has been evaluated as a method to reduce the ovarian toxicity of chemotherapy. The rationale behind this approach is that the degree of gonadal activity at the time of chemotherapy administration appears to correlate with the risk of gonadal failure. For example, studies in children with Hodgkin lymphoma, acute lymphocytic leukemia, and renal disease have suggested reduced gonadal toxicity from chemotherapy in patients who are prepubertal compared with those who are postpubertal at the time of chemotherapy administration. Early studies of ovarian suppression with GnRH agonists during chemotherapy demonstrated high rates of ovarian function preservation in adolescents and young women treated for lymphoma, breast cancer, and other malignancies, including some patients who received high-dose chemotherapy with bone marrow transplantation. The mechanism by which GnRH agonists may protect ovarian function during chemotherapy is uncertain. Although the prepubertal ovary is less active than a mature cycling ovary, follicular growth and atresia have been shown to occur continuously throughout childhood, demonstrating that follicular recruitment can occur independent of gonadotropins. It is unlikely, therefore, that GnRH agonist administration could entirely inhibit follicular atresia. It has been suggested, rather, that GnRH agonists may attenuate follicular atresia through preventing the increase in follicular recruitment and accelerated atresia induced by cytotoxic chemotherapy. Another possible mechanism for the protective effect of GnRH agonists on ovarian function is a reduction in ovarian blood flow as a consequence of inducing a low-estrogen state since ovarian blood flow appears to be increased in the setting of higher estrogen concentrations.

A number of randomized controlled trials evaluating the role of GnRH agonists in reducing ovarian toxicity of chemotherapy have been reported. A variety of surrogate endpoints have been used to assess ovarian function preservation in the trials, including menses recovery, menopausal hormone levels, and measures of ovarian reserve. These endpoints do not necessarily predict pregnancy outcomes or the ideal measure of fertility, and study results have been somewhat conflicting. For example, two positive studies published in 2009 were the ovarian function substudy of the ZIPP trial and an Egyptian trial. In each of these studies, goserelin administration during adjuvant chemotherapy for early-stage breast cancer was associated with higher rates of ovarian function recovery following chemotherapy. In the ZIPP trial, however, the benefit associated with goserelin was not observed in women who also received concurrent tamoxifen.

Another study supporting the use of ovarian suppression during chemotherapy was the PROMISE study, the largest reported randomized trial of GnRH agonist during chemotherapy for protection of ovarian function. In this trial, 281 premenopausal women with stage I to III breast cancer were randomly assigned to receive chemotherapy with or without monthly triptorelin beginning at least 1 week prior to chemotherapy. The investigators observed a significant reduction in the rate of treatment-related early menopause, defined as no resumption of menses (p < .001) and, if available, follicle-stimulating hormone and estradiol in the postmenopausal range at 1 year, with a 25.9% rate of early menopause without ovarian protection compared with 8.9% with the addition of triptorelin to chemotherapy. In 2013, a Chinese randomized phase II trial was reported evaluating leuprolide for ovarian function protection during chemotherapy again in premenopausal women with breast cancer. Among 183 evaluable patients in this study, the rate of early menopause was 16.9% in the leuprolide group compared with 28.7% in the group that received leuprolide without chemotherapy (p < .01).

Three additional randomized trials of GnRH agonists during chemotherapy for breast cancer failed to demonstrate a benefit to the intervention. In a study from UCSF, high rates of recovery of menses were observed following chemotherapy with or without triptorelin and the study was stopped for futility after treatment of just 47 patients. Similarly, in the ZORO study that enrolled 60 patients, rates of menses 6 months after chemotherapy were not significantly different among those who did and did not receive goserelin during chemotherapy and rates of recovery of menses by two years were high in both groups. Despite high rates of recovery of menses, the investigators observed a reduction in ovarian reserve in a subset of 17 patients for whom such measurements were performed with numbers too small to detect a statistically significant difference between those who had received goserelin and those who had not (p = .36). In another Egyptian study, premenopausal women with hormone-insensitive breast cancer were randomly assigned to receive chemotherapy alone or chemotherapy with a GnRH agonist (with or without a GnRH antagonist briefly as well depending on when chemotherapy was initiated). The investigators observed no significant differences with respect to rates of menses resumption or measures of ovarian reserve between the different study arms.

Because patients with breast cancer often receive endocrine therapy following chemotherapy, measuring ovarian function can be challenging in this population. For this reason, the Prevention of Early Menopause Study (POEMS) included only patients with hormone receptor-negative breast cancer. In this study, which was the largest randomized study of a GnRH agonist for ovarian protection that included only patients with hormone receptor-negative breast cancer, a rigorous endpoint of both amenorrhea and postmenopausal hormone levels at 2 years of follow-up was...
used to define ovarian failure.\textsuperscript{99} In the POEMS trial, there was a 70% reduction in the risk of ovarian failure, with 8% of patients on the goserelin arm experiencing ovarian failure compared with 22% on the control arm. In this study, for which data on pregnancy outcomes were routinely collected for 5 years, goserelin use was associated with a significantly higher likelihood of achieving pregnancy after breast cancer treatment (odds ratio 2.23; \( p = .03 \)).\textsuperscript{99}

The OPTION trial was the most recently reported large randomized clinical trial of a GnRH agonist for ovarian protection during chemotherapy for breast cancer. In this trial, there was a significantly lower rate of premature ovarian insufficiency with the use of goserelin during chemotherapy (18.5\% vs. 34.8\%; \( p = .048 \)). A marked reduction in anti-Müllarian hormone levels observed in both study arms, however, raised concerns about the ability of goserelin to protect fertility during chemotherapy.\textsuperscript{100}

Although there have been mixed results from individual studies, meta-analyses of ovarian protection with GnRH agonists during chemotherapy for breast cancer have demonstrated higher rates of menses resumption or reduced risk of ovarian failure with ovarian protection through the use of GnRH agonists during chemotherapy versus without.\textsuperscript{101-103} A recent meta-analysis using individual patient data from randomized trials of GnRH agonists for ovarian function protection in women receiving chemotherapy for breast cancer demonstrated a 62\% reduction in the odds of ovarian failure with the intervention.\textsuperscript{104} This study also confirmed the safety of ovarian suppression with a GnRH analog during chemotherapy in patients with breast cancer, as there was no detriment to disease-free or overall survival outcomes with the intervention regardless of hormone-receptor status.\textsuperscript{104}

Meta-analyses including premenopausal women receiving chemotherapy with or with GnRH agonists for a variety of cancer types in addition to breast cancer have had somewhat different results. An analysis by Elgindy et al that included six breast cancer studies, three lymphoma studies, and one ovarian cancer study concluded that GnRH agonist administration during chemotherapy did not improve the likelihood of ovarian function recovery.\textsuperscript{105} On the other hand, two additional meta-analyses that included patients with a variety of cancer types concluded that GnRH agonist use during chemotherapy was associated with an overall reduced risk of ovarian failure, although in subset analyses, the significant benefit was observed in patients with breast cancer but not for those with lymphoma.\textsuperscript{39,106}

The largest reported randomized study of GnRH agonists for ovarian protection during chemotherapy for women with lymphoma was recently updated.\textsuperscript{107} In this study that included 129 premenopausal women with lymphoma, no significant difference in ovarian failure or pregnancy rates were observed with or without the addition of triptorelin to chemotherapy. Interestingly, study participants in both arms also received norethisterone, a hormonal manipulation that may have provided a protective effect on ovarian function in patients on the control arm.\textsuperscript{107} Although GnRH agonists for ovarian protection currently remain unproven during lymphoma therapy, there is no biologic rationale to suggest that type of malignancy would influence the efficacy of this approach in patients receiving similar types of chemotherapy. Although regimens such as R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, prednisolone) contain drugs at doses similar to what might be used for breast cancer, combinations such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) have been associated with a very low risk for ovarian failure; on the other hand, approaches including high-dose chemotherapy with stem cell transplant are associated with an extremely high risk for ovarian failure. The wide range of gonadal toxicity risk with the various regimens used in the curative-intent setting further complicates our ability to assess the value of GnRH agonists for ovarian protection in patients with lymphoma. Furthermore, differences in patient populations and chemotherapy regimens used with different tumor types make it difficult to generalize the ovarian protective effect of GnRH agonists to disease types other than breast cancer.

Although preventing early menopause is an important endpoint on its own, for women interested in preserving fertility, the ability to achieve pregnancy is a key measure of success of the intervention. A majority of trials evaluating GnRH agonists for ovarian protection have reported numbers of subsequent pregnancies. Among randomized trials of breast cancer that have reported on subsequent pregnancies, there is an approximate 83\% increase in the likelihood of achieving pregnancy with ovarian protection compared with control groups.\textsuperscript{102} A large retrospective cohort study of female patients age 14 to 40 with a variety of cancer types referred to a reproductive endocrinology clinic further supports the theory that protecting ovarian function with GnRH agonists during chemotherapy results in improved fertility prospects.\textsuperscript{108} In this cohort, 122 patients who received GnRH agonist treatment during chemotherapy and 66 patients who received chemotherapy without a GnRH agonist were evaluated for subsequent pregnancy rate. A total of 69.7\% of patients conceived who had received the GnRH agonist compared with 42.4\% of patients who did not receive the intervention (\( p = .003 \)). Differences were also observed in rates of spontaneous conception without ART: 65.6\% of those who received the GnRH agonist compared with 37.9\% of those who did not (\( p = .0004 \)).\textsuperscript{108} These reported pregnancy rates after use of GnRH agonists during chemotherapy compared favorably with those reported after the use of ART in patients with cancer.\textsuperscript{102}

**UTILIZATION OF FERTILITY SERVICES**

Despite the substantial proportion of female patients of reproductive age with cancer who report desiring children, the majority of whom receive cancer therapy that may compromise their fertility, and, despite the availability of ART and ovarian suppression, the uptake of fertility preservation prior to systemic cancer therapy is low. For example, among a population of 1,041 women of reproductive age with a variety of cancer types, 88\% received therapy that could reduce subsequent fertility, but only 4\% pursued
fertility preservation. The most common cancer diagnoses among female patients of reproductive age with cancer who pursue fertility preservation are breast cancer and lymphoma. Among young patients with breast cancer specifically, survey data suggest that only approximately 10% pursue fertility preservation prior to cancer therapy, with some pursuing ovarian stimulation, ovarian suppression, or both. Among patients with lymphoma, ovarian suppression has been the most common approach for fertility preservation to date.

It is likely that multiple factors contribute to the low uptake of fertility preservation among female patients of reproductive age with cancer. Certainly, some patients and oncology providers may be concerned about the impact of delaying cancer therapy to allow for fertility preservation and about the potential impact of fertility preservation on cancer treatment outcomes. However, with timely referral and rapid triage to reproductive endocrinology clinics, fertility preservation can be accomplished quickly. And, although data are limited, ART and ovarian suppression do not appear to increase the risk of cancer recurrence even in the setting of hormone receptor–positive breast cancer.

Despite guidelines intending to standardize care, oncology providers have different practice patterns with regard to referring patients to fertility specialists. For example, female oncology providers are more likely to refer patients to reproductive endocrinology than male oncology providers. Other provider characteristics associated with referring patients to fertility specialists include having a more favorable attitude toward fertility preservation and feeling that patients often ask about the impact of cancer therapy on fertility. Interestingly, although a substantial proportion of patients do not recall discussing fertility issues with their providers, the majority of oncology providers report that they do discuss treatment-related infertility and fertility preservation with their patients; however, only 40% to 50% report always or often referring their patients to fertility specialists. Inadequate knowledge regarding the gonadotoxicity of cancer therapy among oncology providers may also be a barrier to uptake of fertility preservation interventions, as many oncology providers cannot correctly assess a patient’s risk of treatment-related infertility based on treatment regimen and patient age. In addition, some oncologists report personal biases against fertility preservation in certain cases, such as for patients with poor prognoses, which potentially limits referral to fertility specialists. Many oncology providers also lack adequate knowledge of fertility preservation options.

There are also differences in fertility services between cancer centers, potentially related to the practice patterns of oncology providers and availability of fertility specialists. Women who receive cancer care in academic medical centers are more likely to be referred to fertility preservation than women who receive care in community practices. However, even many National Cancer Institute–designated comprehensive cancer centers do not have standard procedures for identification and referral of patients with cancer of childbearing potential to specialists for fertility preservation services.

Although rates of counseling patients about the risk of treatment-related infertility appear to have improved over time, data suggest ongoing disparities. Patients who are older, less educated, and have lower income are less likely to be counseled, whereas those who desire children are more likely to be counseled. Patient factors associated with being referred to a fertility specialist include young age, white race, and not having children prior to cancer diagnosis. Patient characteristics associated with ultimately pursuing fertility preservation interventions include desiring children, not having children prior to cancer diagnosis, higher income, and higher educational attainment. Among patients with breast cancer, pursuit of fertility preservation is less likely among those with a more advanced stage of disease, those who receive neoadjuvant systemic therapy, and those with higher body mass index. Geographic distance from a fertility center does not appear to be a barrier to the pursuit of fertility preservation among patients who see a reproductive endocrinologist, although it may limit referral. Notably, fertility centers that provide a high volume of fertility preservation services in the United States are primarily concentrated in the northeastern regions, suggesting regional disparities in fertility care. Insurance status does not appear to be a barrier to fertility preservation in patients who meet with fertility specialists, although those without insurance may not be referred. The financial burden of fertility preservation is also of concern and may limit uptake of fertility preservation services.

CONCLUSION

Female patients of reproductive age with cancer in the current era are fortunate to have multiple options for fertility preservation. ART is currently endorsed by practice guidelines as the gold standard for fertility preservation patients with cancer. Although the mechanism of action is uncertain and reported findings are not consistently favorable, a substantial body of evidence also supports the use of ovarian suppression for ovarian protection during chemotherapy, especially for patients with breast cancer, and consideration of this approach has been endorsed as an option for fertility preservation by guidelines issued by some organizations, although not fully by ASCO. To date, reported pregnancy rates after ART and ovarian suppression in patients with cancer are similar. Importantly, use of GnRH agonists and ART for fertility preservation are not mutually exclusive, and patients can consider pursuing either option alone or both. Potential considerations regarding the use of GnRH agonists for fertility preservation include lower cost and ease of use, as well as the ability to prevent the consequences of menopause beyond loss of fertility (e.g., vasomotor symptoms, vaginal dryness, loss of bone mineral density). We recommend that oncology providers discuss both ART and ovarian suppression with patients of reproductive age and that the selection of fertility preservation intervention is individualized.
Treatment-related infertility is a significant survivorship issue associated with reduced quality of life, depression, and distress. \textsuperscript{16,35-38} Despite rapidly growing evidence regarding fertility preservation options and treatment guidelines supporting fertility preservation in this population, few patients currently pursue fertility preservation. The oncology community needs to be better educated about treatment-related infertility and fertility preservation options, and information about fertility preservation must be disseminated to patients and their families. Oncologists and fertility specialists must together develop strategies to increase access to and use of fertility preservation by interested patients. Potential strategies to work toward this goal include developing patient educational materials to enhance referrals to fertility specialists, developing institutional fertility programs with dedicated staff to counsel patients and educate oncology providers, developing standardized institutional processes to identify patients who are candidates for fertility preservation, and mandating that oncology providers document discussing fertility issues in the electronic medical record. \textsuperscript{117,122-125} With these strategies and more, together, we can do better.

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The American Joint Committee on Cancer (AJCC) staging system historically has assigned stage on the basis of the size of a patient’s primary tumor, the presence and extent of lymph node disease, and the presence or absence of distant metastasis. The TNM categories are determined, and a corresponding disease stage is defined. At the time of diagnosis, a clinical stage is assigned on the basis of the presenting history, physical examination, and any imaging studies obtained. A pathologic stage, which takes into account the pathologic assessment of the resected tumor and lymph nodes, is assigned after surgery. Although the primary goal of staging is to inform prognosis, staging can also be used to (1) determine a treatment plan, (2) facilitate conversation between providers, (3) identify patient groups for clinical trial participation, and (4) permit standardized data collection that allows for evaluation of the impact of changes in clinical practice.

Since the initial publication of the AJCC staging manual in 1977, the breast cancer staging system has been revised multiple times to reflect advances in diagnosis and treatment. These prior revisions have largely reflected improvements in imaging, surgery, and pathology that have resulted in earlier detection and more refined determination of the disease extent. Previous changes have not accounted for biologic factors like grade, estrogen receptor (ER) status, progesterone receptor (PR) status, and HER2 status, which have predictive and prognostic value. Grade and ER, PR, and HER2 status are determined routinely in the peripheral blood, which is increasingly being evaluated as a compartment that reflects the primary tumor and sites of distant metastases. Diseases should be staged according to the eighth edition staging system to accurately reflect prognosis and to allow standardized data collection. Such standardization will facilitate assessment of the impact of advances in diagnosis and treatment of patients with breast cancer.

INCLUSION OF BIOLOGIC FACTORS IN BREAST CANCER STAGING

Although several groups had questioned the classic anatomic staging system and proposed staging models that incorporated biologic factors to provide more refined prognostic...
information, the AJCC panel did not feel that the available evidence was robust enough to use in the definition of a new staging system. Thus, additional analyses were undertaken to evaluate the prognostic significance of biologic factors in breast cancer by using the National Cancer Database. These data were selected in part because the National Cancer Database includes details for patients treated in approximately 1,500 Commission on Cancer–approved hospitals and so captures greater than 70% of breast cancers diagnosed in the United States. In addition, the majority of patients whose data were captured in the National Cancer Database have been treated with guideline-concordant care that included adjuvant chemotherapy and endocrine therapy when indicated. The analysis undertaken to define the new AJCC staging system included 238,265 patients treated from 2010 to 2011 with complete data, including the new AJCC staging system. Thus, additional analyses were undertaken to define a prognostic stage that was incorporated into the eighth edition of the staging manual, which was published in October 2016. 

An example of how the new staging system is shown in Table 1, which details the pathologic stage groups (i.e., 0, IA, IB, IIA, IIB, IIIA, IIIB, IIIC, and IV). This maintained uniformity with previous editions of the staging system. These stage groups were used to define a prognostic stage that was incorporated into the eighth edition of the staging system, which was published in October 2016. 

The analyses defined combinations of TNM categories with grade and with ER, PR, and HER2 status that could be assigned stage groups (i.e., 0, IA, IB, IIA, IIB, IIIB, IIIC, and IV). This maintained uniformity with previous editions of the staging system. These stage groups were used to define a prognostic stage that was incorporated into the eighth edition of the staging system, which was published in October 2016. 

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Validation of the Eighth Edition of the AJCC Prognostic Stage

After the eighth edition AJCC prognostic stage was published, a validation study was performed with a single-institution cohort from the MD Anderson Cancer Center and a second cohort from the California Cancer Registry population database. The MD Anderson cohort included 3,327 patients treated from 2007 to 2013 with surgery as the initial intervention for stage I to IIIC breast cancer. An important finding was that, in 13.6% (451 patients), no prognostic stage could be assigned because of uncategorized combinations of the biologic factors of grade and ER, PR, and HER2 status with T and N categories (355 patients) or the presence of N1Mi disease in patients with T2 or T3 tumors (96 patients). For those able to have a prognostic stage assigned, stages were upstaged in 29.5% and downstaged in 28.1% compared with the AJCC anatomic stage. Disease-specific survival was determined by both anatomic and prognostic stages. Staging systems were compared using the Harrell concordance index (C index), which can range from 0 to 1 with 0 indicating perfect discordance and 1 indicating perfect concordance. The Akaike information criterion (AIC) was used to compare model fits with a lower AIC indicating a better model. When diseases were staged by the prognostic staging system (AIC = 816.8, C index = 0.8357), there was more refined stratification with respect to disease-specific survival than when diseases were staged by the anatomic stage (AIC = 1039.8, C index = 0.737). In the 54,727-patient cohort identified in the California Cancer Registry, a prognostic stage could not be determined in 6.8% (3,745 patients) because of N1Mi disease in patients with T2 or T3 tumors (1,181 patients) or uncategorized combinations of biologic factors with T and N category (2,654 patients). For those able to have a prognostic stage assigned, 30.9% were upstaged and 20.6% were downstaged. The prognostic stage again outperformed the anatomic stage with respect to stratification by disease-specific survival outcomes (AIC = 80661.68 vs. 81577.89, and C index = 0.8426 vs. 0.8097).

Revisions to the Eighth Edition Prognostic Stage

In response to the finding that a prognostic stage could not be assigned for a percentage of patients, the expert panel revised the eighth edition AJCC breast cancer staging manual. The revision involved repeating analyses with an expanded

### TABLE 1. Pathologic Prognostic Staging for Patients With Anatomic Stage T2N1 Disease

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<th>Grade</th>
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**Abbreviations:** TNM, tumor node metastasis; ER, estrogen receptor; PR, progesterone receptor; Pos, positive; Neg, negative.
Adapted from the American Joint committee on Cancer (AJCC) Cancer Staging Manual, eighth edition.
National Cancer Database data set. This expanded data set included 334,243 patients diagnosed between 2010 and 2012. The median follow-up time was 41.7 months. Two analyses were performed: the first included all patients and was used to define the clinical prognostic stage; the second included 305,519 patients who underwent surgery as their initial intervention and was used to define the pathologic prognostic stage. In both analyses, biologic factors, including grade and ER, PR, and HER2 status, were again combined with TNM categories to define prognostic stage groups. The 3-year overall survival rate was determined for each prognostic stage group and was compared with the seventh edition anatomic stage. If the calculated survival for a prognostic stage group was outside the 95% confidence interval of the seventh edition anatomic stage, then the subgroup was downstaged or upstaged as appropriate. As was done in the first version of the prognostic stage, combinations of TNM and biologic factors were assigned to established stage groups (stage 0, IA, IB, IIA, IIB, IIIA, IIIB, IIC, and IV) on the basis of the survival analyses. In addition, as was established with the initial publication of the prognostic stage, patients with pT1 or pT2, N0, M0, ER-positive, and HER2-negative disease, with an Oncotype DX recurrence score of less than 11 were assigned to pathologic prognostic stage group IA. There is no category to reflect the recurrence score in the clinical prognostic stage table. Using the same cohort of 54,727 patients identified in the California Cancer Registry, we have shown that the revised pathologic prognostic stage continues to stratify patients well with respect to disease-specific survival. As shown in Fig. 1, looking at the hazard ratios, there is a more clear progression with each increasing stage using the pathologic prognostic stage (B) then the anatomic stage (A).

ASSESSMENT OF BIOLOGIC FACTORS

The AJCC prognostic stage incorporates biologic factors that are routinely reported in pathology reports generated for patients with breast cancer. Accurate assessment of these biologic factors, to include determination of grade and ER, PR, and HER2 status, is critical. With respect to grade, use of the Nottingham combined histologic grade is recommended. With that system, a tumor’s grade is determined by assessing morphologic features, including tubule formation, nuclear pleomorphism, and mitotic count, and then assigning a value from 1 (favorable) to 3 (unfavorable) for each. The scores for all three categories are totaled. Grade 1 reflects a combined score of 3 to 5 points; grade 2 is 6 to 7 points; and grade 3 is 8 to 9 points.

The AJCC recommends that ER and PR expression be measured by immunohistochemistry in which any staining of 1% of cells is considered positive, consistent with American Society of Clinical Oncology–College of American Pathologists (ASCO-CAP) guidelines. The reality of ER and PR testing is more complex. In the reporting of ER and, to a lesser extent, PR, multiple scoring systems (e.g., Allred, percentage-positive cells, H Scores) continue to be used. This is in part because the ASCO-CAP panel advises a report of both percentage positivity (percent positive cells) and intensity (average of positively stained cells), which allows considerable flexibility in the reporting system used. To determine simply whether a tumor should be considered positive or negative, this advice may have less impact; however, considerable evidence exists that both the intensity of staining and the percentage of positive cells affects patient prognosis. In one study, patients with 100% of cells staining strongly positive for ER exhibited a 100-fold lower relapse risk than those with 1% positive cells. There is a wealth of data to suggest that ER and PR staining could provide more information about prognosis/treatment outcome than is currently achieved. The future use of automated or semi-automated image analysis platforms has great potential to inform patient and physician choice if they are robustly validated and carefully implemented.

HER2 testing can be done either by immunohistochemistry to assess protein expression or by in situ hybridization to assess gene copy number. Again, ASCO-CAP guidelines should be used to determine HER2 status: immunohistochemistry staining of 0 or 1+ is negative, 3+ is positive, and

![FIGURE 1. Ratios for Disease-Specific Survival for Patients in the California Cancer Registry When Staged According to Their (A) Pathologic Anatomic Stage or (B) Pathologic Prognostic Stage](image-url)
2+ is equivocal.2 Negative in situ hybridization results for laboratories that use dual probes include a HER2/CEP17 ratio of less than 2.0 and HER2 copy number of less than 4 or a HER2 copy number of 4 or greater but less than 6. Possible positive results include a HER2/CAP17 ratio of 2 or greater or HER2 copy number of 6 or greater regardless of ratio. Fewer laboratories use a single probe; in this situation, the cut points are as follows: negative, less than 4 HER2 copies; equivocal, 4 or greater HER2 copies but fewer than 6; and positive, 6 or more HER2 copies. The reality of HER2 testing also is complex. Broadly speaking, the community has been divided between fluorescence in situ hybridization–first or immunohistochemistry-first approaches, and discussions about these choices are rarely based on robust evidence, which, as defined by the ASCO-CAP guidelines, requires validation of test accuracy against an external gold standard. Only two studies have rigorously assessed test accuracy in this way.2,35,36

More critical to patients is the question of so-called rogue cases in HER2 testing reports, which have abnormal/unusual gene amplification patterns.37 Analyzing cases with low HER2 copy number (fewer than four observed copies per cell), but amplified ratios (> 2) is challenging. In 2013, ASCO-CAP followed the global clinical trial evidence, because such patients were included in the pivotal trials and inclusion, in the absence of conclusive data to exclude them, did not change the status of these cases. However, more recent data suggest that these cases infrequently overexpress HER2 at the protein level documented by immunohistochemistry.38 In retrospective unplanned subgroup analyses of clinical trial data, patients with these HER2 testing results did not show hazard ratios consistent with response to trastuzumab.38 This observation has driven a change in ASCO-CAP guidance, such that the 2018 panel suggests that tumors with these results “should no longer be considered HER2-positive unless IHC3+ overexpressed” (personal communication, J.M.S.B.). Fortunately, these cases are rare (<1% of all amplified cases); nonetheless, they do present a clinical dilemma with little robust evidence to direct treatment choices. Additional research into the true cytogenetic make up of these cases is required if we are to reach a position in which treatment can be driven by robust evidence. What makes this setting more challenging is the potential heterogeneity within this group, which may well represent both cases with intrachromosomal amplification of HER2 (in one chromosome) with a concordant deletion within the sister chromosome and those with low-level CEP17/HER2 duplication. Although ASCO-CAP and others have provided guidance, research into the underlying molecular causes for some rogue results remains a priority to provide additional support for treatment decisions. It is worth noting that, although some multigene signatures may report HER2, (or ER/PR) results, evidence suggests that these are not accurate surrogates for appropriate in situ testing of receptor status.39,40

In parallel, there has been continued discussion regarding the impact of HER2-targeted therapeutics, specifically trastuzumab, in low copy about/amplified cases. This conversation has been stimulated by cases in the original phase II/III trials that, on retesting in central laboratories, were reclassified as HER2 negative.41-43 These cases sparked considerable debate, because they had previously been reported as HER2 positive elsewhere, often in equally reputable laboratories. This ultimately sparked a randomized clinical trial (NSABP B47) to evaluate the use of trastuzumab in patients with tumors determined to be 1+ or 2+ by immunohistochemistry. The results of this trial, reported at the 2017 San Antonio Breast Cancer Symposium, showed no benefit from trastuzumab in patients with low HER2–expressing tumors.44 From a pathologist’s perspective, the findings from this study are likely not indicative of some strange underlying, and consistently elusive, biology of cases that have discrepant results. No laboratory test is 100% accurate, and any retesting of samples is likely to reveal discrepancies that are no more than the play of chance. A remaining unanswered paradox in HER2 testing is the determination that a HER2/CAP17 ratio of 2.1 is positive, but ratios of 1.9 are negative. All the ramifications of this cut point are not yet fully understood.

Receptor Testing: Perils, Pitfalls, Controversies, and Best Practices

Although testing for receptors has long been part of the diagnostic evaluation of breast tumors (ER and PR testing was initiated in the 1970s; HER2 testing, in the 1990s), debate persists. In addition, during the last 40 to 50 years, there have been faults and errors in receptor testing that led to failures in diagnostic delivery for patients and resulted in key lessons learned. Faults developed from defects in processes or systems that led to failures. Errors developed as a result of deviations from required or optimal operational processes. Those involved in diagnostic testing for receptors must be on guard constantly for both system defects and deviations. This need for vigilance was confirmed in the late 2000s, when issues were noted that had a great impact on multiple patients.45,46 Before these issues occurred, efforts to develop processes and guidelines to ensure that diagnostic tests were performed to the highest standard were patchy. Literature detailing evidence on quality challenges and system failures seemed to have gone largely unnoticed in some countries, whereas other countries were implementing rigorous quality assurance programs and guidelines as early as 2000.47-50 Although hindsight is a poor perspective to reflect on past processes, certainly there are lessons to be learned from these events that brought issues of quality, consistency, and accuracy to the forefront for both novel and established tests—for example, current multigene prognostic signatures. Indeed, the field of receptor measurement has been changing continually in response to challenges posed by demands for improved accuracy, reproducibility, and greater diagnostic value from the simple analytic technologies applied to receptor testing.

As a result of previous challenges and controversies, robust and well thought out guidelines or recommendations exist in most jurisdictions to promote best practice. Although not every statement in these documents has the preferred
robust evidence base, the documents nonetheless represent a distillation of current best evidence and experience. They provide the best processes designed to support current diagnostic practice and should be read, understood and implemented by pathologists who assess breast tumors. Challenges that are based on new evidence and understanding will drive continued revision and improvements in these documents and the associated processes. In the meantime, adherence to guidelines will reduce the faults in our systems and provide best-practice diagnostic approaches. In parallel, adherence to best practices thorough monitoring, testing, and quality assessments of results provides the optimal approach to preventing, identifying, and correcting errors in the implementation of systems. Constant monitoring of protocol adherence and performance internally (through process audits, supportive management structures, internal quality assessment) is essential if continued quality is essential to maintain a safe and effective service, but—in diagnostic quality monitoring as in medicine—prevention is better than cure.

DIAGNOSTICS IN 2020: WHAT ABOUT THE FUTURE?
Assays to Determine Receptor Status
Perhaps the most surprising thing about diagnostic testing for receptors in breast cancer is not what has change but what has not. Fundamentally the same technology used to detect ER and PR status that was originally applied in the 1970s is still relied upon. For almost 50 years, the basic methodology has remained unchallenged, without fundamental changes in approach. Does this mean that change is unlikely in the future? On the contrary, advances in molecular technologies and image analysis approaches arguably make change more likely now than ever before. One question is, which approach will win out? Will quantitative image analysis provide increasing granularity of information on the basis of existing in situ approaches, perhaps with increasing multiplexing, quantitation, and information for patients? Or will molecular approaches, using mRNA-based analytic approaches, finally succeed in supplanting in situ microscopy-based solutions? Both approaches have growing evidence to support them, and methods to perform diagnostically robust analyses for ER/PR and HER2 status with these approaches now exist, as evidenced by the large prognostic impact of these markers measured at the RNA level.\(^\text{35-58}\) When future guidelines from ASCO-CAP are developed, and when subsequent iterations of the AJCC staging are discussed, careful review of these approaches must be undertaken to determine if evidence supports additional recommendations for their use. These technologies may represent a solution to challenges related to receptor testing not only in low-income but also high-income countries.

Beyond the Tissue
In recent years, advances in technology to reliably detect cancer associated alterations in the blood have challenged the notion that anatomic and radiographic measures can comprehensively profile the disease states. There is, of course, a long history of incorporating blood-based measures of extent of disease in other solid tumors, such as in germ cell tumors or prostate cancer. In the case of breast cancer, however, such protein-based assays have not proven sufficiently beneficial to recommend their common use. Indeed, ASCO guidelines only support use of these in metastatic disease.\(^\text{6}\) However, the sensitivity and specificity for newer blood-based assays may well be significantly higher than those of previous tumor markers, primarily carcinoembryonic antigen and cancer antigen 15-3. In particular, ctDNA and circulating tumor cells (CTCs) have been identifiable in many patients whose tumors lacked elevated tumor markers.\(^\text{59}\) Moreover, these cells may inform more than simply the presence or absence of disease but may have the potential to be quantified and to provide information about the molecular features of the disease. The ability to molecularly classify the disease (e.g., identifying panels of specific mutations or features of CTCs) may provide substantial benefits but goes beyond the scope of this discussion of its value for staging and extent of disease assessment. For the purposes of tumor staging, it is essential that ctDNA or CTC assays (1) perform reproducibly across large studies, (2) have sufficient sensitivity and specificity to identify disease where conventional anatomic or radiographic does not, and (3) provide strong enough independent prognostication to potentially enable predictive ability.

Disseminated tumor cells. In a pivotal analysis, Braun et al\(^\text{60}\) combined data from nine studies of micrometastatic breast cancer in bone marrow among patients with early-stage disease and found that the presence of micrometastases (as defined positive in each study) was associated with breast cancer recurrence and mortality. This association was independent of other prognostic factors. However widespread adoption of such a test did not take place because of its invasive nature, the lack of predictive utility, and the subsequent development of gene expression arrays as a distinct method for prognostication and use in prospective studies.

CTCs. Similarly, the presence of CTCs in nonmetastatic breast cancer has been associated with inferior disease-free survival in numerous studies, including one study of more than 2,000 patients that used the CellSearch system for CTC detection.\(^\text{61}\) However, many of these studies had short follow-up times relative to the recurrence of breast cancer, and the ability to prognosticate recurrence for small, node-negative tumors or those of the luminal subtype was less apparent.\(^\text{13}\) In addition, several studies have examined the utility of clearance of CTCs with therapy (e.g., chemotherapy) as a means of prognosticating outcomes. Once again, the effect
of persistent detection of CTCs has been reported in numerous studies, albeit with smaller numbers and shorter follow-up time. What these studies revealed was the potential for this modality to provide independent prognostic ability from conventional measures. Weighed against this power has been the relatively low sensitivity (historically) and variability of methods for detecting CTCs. Even more important, it remains unclear whether even more sensitive and uniform measures of CTCs ultimately can predict the value of additional monitoring or therapy and thereby have the potential to improve outcomes—particularly for HR-positive/HER2-negative tumors for which gene expression profiling is now standard of care. One promising application in this regard may be in the assignment of extended adjuvant hormonal therapy (years 5–10) where a recent study identified CTC positivity in approximately 5% of patients after 5 years of adjuvant therapy, and this positivity was associated with a 20-fold increased risk of subsequent recurrence.62

ctDNA. Assays to detect ctDNA among patients with cancer are under intense technologic development. The ability of either sequencing or methylation of DNA fragments found in blood to reliably and sensitively detect breast cancer in advanced-stage disease has been reported by many groups.59,63–65 Indeed, small studies to compare ctDNA and CTCs have hinted at greater potential sensitivity for ctDNA in this setting.66 Many of the advances in this area have come with increasing power and decreased cost of DNA sequencing; thus, mature clinical data in the early-stage setting are not available. Moreover, the quantity of DNA shed by tumor cells into circulation among patients with early-stage disease is considerably lower than the quantity in metastatic disease. This leaves open the question of whether this method can be used reliably to prognosticate outcomes for a large enough percentage of patients with early-stage disease. Moreover, there are wide differences in the techniques used for evaluating tumor DNA, some of which are less sensitive but provide information about a large number of genes (whole-exome sequencing); some of which rely heavily on a priori knowledge of the tumor alterations present in a tumor biopsy (e.g., droplet digital polymerase chain reaction); and some of which provide almost no added information about the somatic mutations present, even if positive (methylation).

Weighed against these important caveats about use of CTCs or ctDNA in staging disease in patients is the plethora of new modalities of systemic therapy potentially available beyond standard endocrine and chemotherapy. Some of these are highly effective only in subsets of patients with metastatic disease (e.g., PARP inhibitors in germline BRCA-mutant cancer) but are unlikely to provide added value to the entire group of patients who receive standard-of-care treatments that already result in high cure rates for the overall population. The ability of either CTCs or ctDNA to profile minimal residual disease or disease nonresponsive to conventional treatments should enable rapid testing of new agents among groups that are undoubtedly at high risk. Moreover, the ability of these tests to provide qualitative information (e.g., genomic profile or heterogeneity of immunohistochemistry positivity for ER/HER2), may enable use of agents not possible by conventional assays of the tumor itself. Indeed, the increasing insights we now have on widespread heterogeneity of breast tumors provide the biologic rationale for this type of approach. Metastatic recurrences can differ from primary tumors in transcriptional or genomic profile in many cases—to the degree that liquid biopsies are sensitive enough to profile the minimal residual disease that lead to such recurrences—so that new tests may enable more effective use of many agents that would not otherwise be practical in the early-stage setting. Such practice-changing information would constitute an essential part of defining the extent of disease and should necessarily be included in any meaningful staging system.

CONCLUSION

With the eighth edition of the staging manual, the AJCC has recognized the impact of biologic factors in determining treatment plans and prognoses for patients with breast cancer. Better stratification for survival outcomes can be achieved by using the clinical and pathologic prognostic stages that combine the anatomic extent of disease with biologic factors to include grade and ER, PR, and HER2 status. This initial effort to incorporate tumor biology into staging was deemed critical to preserve relevance of the staging system. Accuracy of staging is dependent on rigorous determination of the biologic factors and guideline-concordant treatment dictated by those factors. As technology evolves to allow more refined determination of tumor biology and to assess how the refined determinations affect treatment and outcomes, the staging system will require more revision. Currently, however, diseases should be staged according to the eighth edition of the clinical and pathologic prognostic stages to acquire the necessary data to inform future revisions.

References


44. Fehrenbacher L, Cecchini RS, Geyer CE, et al. NSABP B-47 (NRG Oncology): phase III randomized trial comparing adjuvant chemotherapy with adriamycin (A) and cyclophosphamide (C) → weekly paclitaxel (WP), or docetaxel (T) and C with or without a year of trastuzumab (H) in women with node-positive or high-risk node-negative invasive breast cancer (IBC) expressing HER2 staining intensity of IHC 1+ or 2+, with negative FISH (HER2-low IBC). Abstract presented at: San Antonio Breast Cancer Symposium; 2017; San Antonio, TX.


The use of a neoadjuvant therapeutic approach in patients with breast cancer has become more widespread over the last decade. Although the primary purpose for using preoperative therapy is to downstage breast cancers, allowing for a less-aggressive surgical approach, its use additionally allows an in vivo assessment of whether a therapeutic approach is effective in an individual cancer without increasing the risk of distant recurrence.³

The acquisition of a pathologic complete response (pCR) using a definition of no invasive cancer in the breast or lymph nodes following preoperative chemotherapy with or without HER2-directed agents has been demonstrated to be a robust prognostic factor, especially for HR-negative and HER2-positive breast cancers.² In 2013, the U.S. Food and Drug Administration (FDA) for the first time approved the use of an agent, pertuzumab, based on the findings that pCR was significantly increased when it was added to trastuzumab-based chemotherapy in patients with HER2-positive breast cancer.³,⁴ Trials evaluating neoadjuvant therapies require considerably smaller numbers of patients with inherent reduced cost compared with larger adjuvant studies. Additionally, the use of pCR as a surrogate endpoint for longer-term outcomes allows the efficacy of a given agent to be determined relatively rapidly, compared with many years in adjuvant studies. Overall this approval by the FDA opened the door for the potential of accelerated approval of new agents for patients with earlier-stage breast cancers.

However, the use of pCR as a surrogate for efficacy of novel agents remains controversial, in part because available preoperative trials were not powered to evaluate longer-term endpoints such as event-free and overall survival (OS). In fact, the majority of preoperative trials have not demonstrated an improved outcome for the new agents being evaluated, although pCR remains prognostic.³,⁵ Additionally, positive findings noted in the preoperative setting have not been definitely confirmed in larger adjuvant trials.¹⁰,¹¹ Lastly, the prognostic ability of pCR is different based on breast cancer subtypes: pCR is prognostic in TNBC, HER2-positive, and luminal B breast cancers, although it is not definitively prognostic in luminal A cancers, the latter of which present a significant therapeutic challenge given their lack of response to preoperative chemotherapy.²,¹² Given the lack of benefit from preoperative chemotherapy in HR-positive breast cancers, especially those with a luminal A phenotype, there...
has been significant interest in evaluating preoperative endocrine therapeutic approaches. However, interpretation of results from trials evaluating preoperative endocrine therapies with or without targeted agents has been hampered by determining an appropriate endpoint, because obtaining a pCR is rare. Generally, accepted endpoints for preoperative endocrine therapy trials include changes in Ki-67 following 2 weeks of therapy, and the PEPI score, which estimates the amount of residual cancer left following therapy.

We will review the use of a preoperative approach in evaluating new agents in different breast cancer subtypes: HR-positive, TNBC, and HER2-positive breast cancers.

**NEOADJUVANT ENDOCRINE THERAPY**

Perhaps no other area of breast oncology has undergone such a dramatic change in practice as the use of chemotherapy for HR-positive disease. Prior to the advent of multiparameter gene expression assays, consensus guidelines routinely recommended chemotherapy for all patients with a primary tumor spanning at least 1 cm. Although subset analyses of large trials suggested the benefit of adjuvant chemotherapy was primarily (if not entirely) in those with poorly differentiated tumors, lower levels of HR expression, or overexpression of HER2, most oncologists feared withholding the potential benefits of chemotherapy more than they feared the toxicity associated with overtreatment. The multiparameter assays more convincingly identified patients who would not benefit from chemotherapy, resulting in a significant reduction in the use of chemotherapy for early-stage hormone-sensitive disease. The (re)appreciation of the benefit of hormone therapy led naturally to reconsidering the role of hormone therapy prior to surgical resection.

NET in this context must be distinguished from the use of hormone therapy alone (that is, primary hormone therapy prior to surgical resection). NET can facilitate breast-conserving surgery focused on intermediate biologic endpoints obtained from the surgical specimen or via serial biopsy of the primary tumor.

The increased pCR rate noted with novel therapies in the increased pCR rate noted with novel therapies in the preoperative setting has not routinely translated into improved event-free, disease-free, or overall survival. Many HR-positive breast cancers, especially luminal A cancers, have a minimal response to preoperative chemotherapy, and pCR in this scenario is not associated with outcome. The use of NET is a consideration for patients with HR-positive cancers, who are candidates for a preoperative approach. Changes in Ki-67 and the PEPI score are reasonable surrogates of outcome in patients with HR-positive cancers treated with NET.

**IMPACT Trial**

The IMPACT trial compared the preoperative use of tamoxifen with anastrozole alone or in combination in postmenopausal women (330 patients) with primary HR-positive breast cancer. The investigators hypothesized that the clinical and/or biologic effects of NET would predict long-term outcome in the Anastrozole, Tamoxifen Alone or in Combination (ATAC) adjuvant therapy trial. The clinical hypothesis proved false, as there were no significant differences in overall response or the proportion of patients able to undergo BCS in IMPACT. Importantly, IMPACT included the collection of tissue specimens taken at baseline, and after 2 and 12 weeks of treatment to explore biologic correlates of long-term outcome. Here the hypothesis proved correct. A decrease in the proliferation marker Ki-67 occurred in the majority of patients. However, there was a significantly greater suppression of Ki67 in the anastrozole-treated group than in the tamoxifen- or combination-treated groups. Estrogen-receptor (ER) level correlated with Ki67 suppression; that is to say that tumors with higher ER expression tended to have greater suppression of proliferation with NET. Progesterone-receptor (PR) expression was important to chemotherapy. Particularly for postmenopausal women with clinical stage II/III hormone sensitive breast cancer, NET remains an underused and less-toxic alternative to neoadjuvant chemotherapy.

Some benefits of NET replicate those of neoadjuvant chemotherapy. NET can facilitate breast-conserving surgery (BCS). Half of patients destined for mastectomy are able to undergo BCS after 3 to 4 months of aromatase inhibition. Patients concerned about a delay in treatment while waiting for results of genetic testing or surgical scheduling can safely begin NET.

Although most NET trials gave therapy for 3 to 4 months, the optimal duration of treatment has not been fully established. A multicenter single-arm trial investigated the effect of neoadjuvant treatment duration on tumor regression and ability to undergo BCS. The majority of partial or complete responses were observed at 4 months, though some beneficial responses occurred during prolonged letrozole treatment. Compared with baseline, median tumor size was reduced by 62.5% at month 4 and by 70.0% at final study visit (8 months). Even though prolonged treatment of up to 8 months resulted in further tumor volume reduction in some patients, there was no clear optimum for treatment duration. Outside of a clinical trial, 4 months is a reasonable starting point with the option to continue treatment in responding patients who desire BCS.

Neoadjuvant chemotherapy allows an individual assessment of response based on pathologic response. PCR rates are low with NET, limiting the value of pCR as a surrogate endpoint for the effectiveness of NET. Instead, efforts focused on intermediate biologic endpoints obtained from the surgical specimen or via serial biopsy of the primary tumor during treatment. We will now focus on using NET as an individual in vivo sensitivity test.
as well, with a greater reduction in proliferation in tumors that expressed PR. In a multivariable analysis, higher Ki-67 expression after 2 weeks of NET was associated with lower recurrence-free survival (p = .004) whereas higher Ki-67 expression at baseline was not. Larger baseline tumor size and lower ER level after 2 weeks of NET were also associated with poorer recurrence-free survival (p < .001 and p = .04, respectively).22 NET did not increase apoptosis, so cell loss is primarily due to natural attrition; clinical response is dependent on the antiproliferative effect of estrogen withdrawal.23 Together these data highlight the potential value of Ki-67 as a marker of endocrine therapy benefit.

Preoperative Endocrine Prognostic Index

PEPI was developed to identify patients with such dramatic sensitivity to endocrine therapy that chemotherapy could be avoided. It incorporates features from initial diagnosis (prior to NET) and response to NET to separate patients into prognostic groups. Patients with a primary tumor smaller than 5 cm, negative nodes, and a Ki-67 less than 2.7% after NET are in the lowest risk PEPI group (PEPI = 0).24 PEPI predicted long-term outcome in patients treated with neoadjuvant aromatase inhibition in the Z1031 trial. With a median 5.5 years of follow up, 3.7% of patients (4 of 109) with a PEPI of 0 relapsed compared with 14.4% of patients (49 of 341) with a PEPI greater than 0 (recurrence HR 0.27; p = .014).25

A major drawback of relying on PEPI is that results are not known until patients have completed 4 months of endocrine therapy and undergone surgery. That feels like a long time to wait for patients and their treating physicians. Importantly, there is no way to assess response to subsequent chemotherapy (or any other treatment of that matter) as the primary tumor has already been removed. Ideally, we would identify patients with resistant disease earlier so chemotherapy (or another alternate treatment) could be given prior to surgery. Data from the IMPACT22 and POL26 trials found that patients with a Ki-67 greater than 10% after only 2 to 4 weeks of NET were extremely unlikely (< 2%) to achieve a PEPI of 0. Lack of dramatic response to endocrine therapy does not necessarily mean that those patients will benefit from chemotherapy. In fact, the limited available data suggest that patients with Ki-67 greater than 10% after 2 to 4 weeks of NET respond poorly to neoadjuvant chemotherapy. Only 5.7% of patients (2 of 35) in the Z1031B trial who switched to neoadjuvant chemotherapy achieved a pCR.25

Evaluation of Novel Therapies

PEPI may help identify more effective endocrine therapies, using the proportion of patients who achieve a PEPI of 0 as a surrogate endpoint. The ALTERNATE trial (NCT01953588) uses this strategy, comparing anastrozole, fulvestrant, or the combination. Eligible patients are postmenopausal and have palpable ER-positive tumors with an Allred score of 6 to 8. As with the prior Z1031 trial, chemotherapy is recommended in patients with a Ki-67 greater than 10% after 2 to 4 weeks.

NET can also be used as a platform to which to add novel therapies in patients with ER-positive disease. Here are a few examples of the many trials evaluating novel agents in the NET setting. One early effort investigated whether neoadjuvant gefitinib, an EGFR inhibitor, might overcome biologic and clinical resistance to NET in a phase II placebo-controlled trial.27 In addition to anastrozole, patients were randomly assigned to receive either gefitinib 250 mg/d orally for 16 weeks, placebo for 2 weeks followed by gefitinib for 14 weeks, or placebo for 16 weeks. The primary endpoint was change in proliferation (Ki-67) at 2 and 16 weeks. Mean changes in Ki-67 with anastrozole and gefitinib versus anastrozole alone were -80.1% and -71.3% respectively between baseline and 2 weeks (geometric mean ratio, 0.70; p = .22) and -77.4% and -83.6% between baseline and 16 weeks (geometric mean ratio, 1.37; p = .26). Clinical response rate also favored anastrozole alone (61% vs. 48%), though the difference was not statistically significant (p = .08).

Hyperactivation of AKT is common and is associated with endocrine resistance in ER-positive breast cancer. A randomized phase II trial tested the hypothesis that adding the allosteric pan-AKT inhibitor MK-2206 to anastrozole would increase pCR in PIK3CA-mutant, ER-positive breast cancer.28 Patients received endocrine therapy alone for 28 days (to allow for PIK3CA analysis); then MK-2206 was added on cycle 1 day 2 (C1D2) in patients with tumors positive for PIK3CA mutation. Patients received a maximum of four 28-day cycles of combination therapy before surgery. Serial biopsies were collected at preregistration, C1D1 and C1D17. Of 51 patients preregistered, 22 had a PIK3CA mutation. Sixteen began MK-2206; three stopped therapy early because of persistent elevation of Ki-67 (two patients) and toxicity (one patient). Thirteen patients completed neoadjuvant therapy followed by surgery, but none achieved a pCR. Importantly, MK-2206 did not further suppress proliferation (Ki-67) and did not induce apoptosis on C1D17 biopsies. The investigators concluded that MK-2206 was unlikely to add to the efficacy of anastrozole alone in PIK3CA-mutant, ER-positive breast cancer and should not be studied further in the target patient population.

In the NeoPalAna29 trial, patients underwent a pretreatment biopsy, and then treated with anastrozole for 1 month. After a second biopsy, palbociclib was added to anastrozole with a third biopsy obtained 14 days later. Primary endpoint was suppression of Ki-67 to less than 2.7% at any time point. Palbociclib increased the proportion of patients with a Ki-67 response. Interestingly, in some patients, anastrozole alone suppressed Ki-67, whereas in others, combined therapy did not suppress Ki-67. Investigators also explored serum thymidine kinase 1 (TK1) as a measure of proliferation and activity of the CDK4/6 inhibitor.30 Despite a significant drop in tumor Ki-67 with anastrozole monotherapy, there was no statistically significant change in TK1 activity. However, a striking reduction in TK1 activity was observed 2 weeks after initiation of palbociclib (C1D15), which then rose significantly with palbociclib washout. There was high concordance between changes in serum TK1 and tumor Ki-67. They concluded
that serum TK1 activity might be a promising pharmacodynamic marker of palbociclib in ER-positive breast cancer. Though not directly addressed in the NeoPalAna trial, these results highlight the potential for early assessment of NET response, whether with serial biopsy or serial serum TK1, to individualize therapy.

**TRIPLE-NEGATIVE BREAST CANCER**

In most series including the FDA meta-analysis,1,2 pCR has been demonstrated to be prognostic for outcome in patients with TNBC. This led to trials evaluating the addition of chemotherapy and novel agents to standard chemotherapy in the preoperative TNBC setting, using pCR as a primary endpoint. In general, though pCR was found to be prognostic in most of these trials, they have not shown conclusively that the novel agents improved longer-term outcomes.7,9 The residual cancer burden (RCB)31 is used to quantify the amount of cancer remaining in patients who have received preoperative therapy. Patients with TNBC who achieve RCB 0 (pCR) or RCB 1 (minimal residual disease) appear to have a favorable outcome, whereas those with RCB 3 (minimal response to chemotherapy) have an alarmingly high rate of relapse.32 Given the high relapse rate seen in patients with TNBC whose cancers fail to respond to preoperative chemotherapy, there is considerable research focus on evaluating agents, such as other chemotherapeutics, targeted agents, and immune therapies, in the postsurgery “adjuvant” setting. The CREATE X trial33 is the first trial to demonstrate an improved disease-free and OS for patients with TNBC with residual cancer following preoperative chemotherapy who received adjuvant capecitabine. However, it is clear that there are patients with TNBC who do not achieve a pCR who do not experience a subsequent relapse, and, conversely, relapses have been seen in patients who achieve a pCR. This may in part be explained by the fact that TNBC is known to be a heterogeneous disease, comprising several different subtypes35 with differential response rates to preoperative chemotherapy. For example, the luminal androgen receptor TNBC subtype has a low response rate to preoperative chemotherapy,35 but pCR is not as robust a prognostic factor as it is for other TNBC subtypes.36

**TABLE 1. Efficacy of Standard Anthracycline-Taxane Chemotherapy in TNBC Subtypes34,35**

<table>
<thead>
<tr>
<th>Subtype</th>
<th>No. of Patients</th>
<th>pCR, %</th>
<th>95% CI</th>
</tr>
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<tbody>
<tr>
<td>Basal-like 1</td>
<td>21</td>
<td>52</td>
<td>0.31–0.73</td>
</tr>
<tr>
<td>Basal-like 2</td>
<td>8</td>
<td>0</td>
<td>0.00–0.00</td>
</tr>
<tr>
<td>Mesenchymal</td>
<td>26</td>
<td>31</td>
<td>0.13–0.48</td>
</tr>
<tr>
<td>Mesenchymal stem cell-like</td>
<td>13</td>
<td>23</td>
<td>0.0001–0.45</td>
</tr>
<tr>
<td>Immunomodulatory</td>
<td>27</td>
<td>30</td>
<td>0.12–0.46</td>
</tr>
<tr>
<td>Luminal AR</td>
<td>20</td>
<td>10</td>
<td>0.03–0.23</td>
</tr>
</tbody>
</table>

**Abbreviations:** TNBC, triple-negative breast cancer; pCR, pathologic complete response; AR, androgen receptor.

The current standard preoperative approach for patients with TNBC remains an anthracycline taxane–based regimen. Substitution of paclitaxel with nab-paclitaxel followed by epirubicin and cyclophosphamide demonstrated a pCR rate of almost 50%37 and improved disease-free survival for patients with TNBC receiving nab-paclitaxel,8 though these results are not confirmed in a similar trial39 (Table 2). The addition of carboplatin to an anthracycline-taxane backbone has been demonstrated to improve pCR in several trials,39,40 though this did not routinely result in improved outcome, likely due to the trials’ power9 (Table 2). The I-SPY 2 trial41 provides a unique platform using an adaptive design for evaluating the addition of novel agents to anthracyclines and taxanes in high-risk early-stage breast cancer. To date, this trial has “graduated” two agents in TNBC based on predicted pCR rates, meaning that they warrant further evaluation. In I-SPY 2, the addition of veliparib to paclitaxel followed by adriamycin-cytoxan was associated with an estimated PCR of 51%42 and the addition of pembrolizumab resulted in an estimated PCR of 60%43 in patients with TNBC. Overall, the preoperative setting provides a unique method of assessing the efficacy of novel agents in TNBC, when added to standard chemotherapy (Table 2).

Given the high rate of relapse in patients with TNBC who do not achieve a pCR or near-pCR following preoperative chemotherapy,35 there is considerable interest in adjuvant approaches to reduce the risk of recurrence. To date, the only successful approach is with the use of capecitabine given for eight cycles following surgery. The CREATE-X trial43 randomly selected patients with HER2-negative cancers and residual disease following preoperative chemotherapy to receive standard therapy alone or capecitabine for eight cycles in addition to standard therapy. In patients with TNBC, DFS, and OS were significantly improved in patients who received capecitabine compared with the control group. These results were somewhat surprising given the chemotherapy-resistant nature of the majority of TNBC that do not respond to standard preoperative therapy. There are a number of clinical trials evaluating novel approaches in the post-preoperative therapy setting. The ECOG-ACRIN 1131 trial was initially designed to evaluate the use of a platinum, either carboplatin or cisplatin compared with no further systemic therapy, in this setting, but was modified after the results of CREATE-X were reported to compare a platinum agent to capecitabine (NCT02445391). SWOG-S1418/NRG-BR006 (NCT02954874) is evaluating pembrolizumab versus no further therapy in patients with residual TNBC following preoperative therapy. Investigators at Indiana University are taking a novel approach of genomically typing residual TNBC following preoperative chemotherapy, and then matching the results with agents given adjuvantly (NCT02101385).

**PREOPERATIVE APPROACHES IN HER2-POSITIVE BREAST CANCER**

Trastuzumab therapy is one of the most impactful therapeutic advances in breast cancer. It is well established that incorporation of 1 year of trastuzumab in addition to
patients were assigned to receive trastuzumab, lapatinib, or pertuzumab; pemb, pembrolizumab; nabP, nab-paclitaxel; EC, epirubicin-cytoxan; FEC, 5-fluorouracil, epirubicin, cytoxan; N/A, nonapplicable; NS, nonsignificant.

Anthracycline-Taxane Chemotherapy on pCR in TNBC

A uniform definition of pCR. 2 Personalizing therapy based on pCR may help us stratify which patients need additional therapy alone, at a median follow-up of 4.5 years.10

Despite significant doubling of the pCR rate, (51.3% in the combination vs. 29.5% in the trastuzumab-only group 51; p = .0001), this did not translate into improved survival in the combination group.5 One caveat is that all patients received further systemic therapy after surgery. Therefore, the pCR rates in each of the arms did not reflect the response to all the therapy that these patients received. NeoALTTO, however, demonstrated that women who achieved a pCR had significantly better 3-year event-free survival (HR 0.38; p = .003) and OS (HR 0.35; p = .005) than those who did not achieve a pCR.5 In keeping with the overall outcomes noted in NeoALTTO, the ALTTO trial, a large adjuvant trial that enrolled 8,381 patients, did not note a significantly improved outcome for the addition of lapatinib to trastuzumab-based chemotherapy, compared with trastuzumab-based chemotherapy alone, at a median follow-up of 4.5 years.10

Neratinib is an irreversible pan-HER2 tyrosine kinase inhibitor. In the I-SPY 2 trial,41 patients with HER2-positive breast cancer were randomly assigned to receive weekly paclitaxel with neratinib for 12 weeks, or weekly paclitaxel with trastuzumab, followed by four cycles of doxorubicin and cyclophosphamide. The estimated pCR rate in the neratinib arm was 56% (95% CI, 37%–73%) compared with 33% on the trastuzumab arm (95% CI, 11%–54%) in patients with HR-negative, HER2-positive tumors,52 allowing neratinib to graduate to a confirmatory phase III trial. The efficacy of neratinib in the early-stage HER2-positive setting was further confirmed in the ExteNET trial, which evaluated the role of neratinib as extended adjuvant HER2-directed therapy in patients who had completed 1 year of adjuvant trastuzumab.53 After a median follow up of 5.2 years, patients in neratinib group had significantly fewer invasive DFS events than those in the placebo group with a hazard ratio of 0.73, (p = .0083). The 5-year invasive DFS was 90.2% (95% CI, 88.3%–91.8%)

Tyrosine Kinase Inhibitors

Lapatinib is a small molecule dual tyrosine kinase inhibitor targeting the epidermal growth factor and HER2. The NeoALTTO trial,4 a phase III randomized trial (neoadjuvant lapatinib and/or trastuzumab treatment optimization), evaluated neoadjuvant lapatinib and trastuzumab combination therapy, compared with single-agent HER2-directed therapy, in HER2-positive operable breast cancer. A total of 455 patients were assigned to receive trastuzumab, lapatinib, or a combination of the two agents in addition to paclitaxel. Despite significant doubling of the pCR rate, (51.3% in the combination vs. 29.5% in the trastuzumab-only group51; p = .0001), this did not translate into improved survival in the combination group.5 One caveat is that all patients received further systemic therapy after surgery. Therefore, the pCR rates in each of the arms did not reflect the response to all the therapy that these patients received. NeoALTTO, however, demonstrated that women who achieved a pCR had significantly better 3-year event-free survival (HR 0.38; p = .003) and OS (HR 0.35; p = .005) than those who did not achieve a pCR.5 In keeping with the overall outcomes noted in NeoALTTO, the ALTTO trial, a large adjuvant trial that enrolled 8,381 patients, did not note a significantly improved outcome for the addition of lapatinib to trastuzumab-based chemotherapy, compared with trastuzumab-based chemotherapy alone, at a median follow-up of 4.5 years.10

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### TABLE 2. Selected Trials Evaluating the Efficacy of the Addition or Substitution of New Agents to Standard Anthracycline-Taxane Chemotherapy on pCR in TNBC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Arms</th>
<th>pCR</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calgb 4060349 (443 Patients)</td>
<td>P → AC</td>
<td>41%</td>
<td>p = .0029</td>
</tr>
<tr>
<td></td>
<td>PCBb → AC</td>
<td>54%</td>
<td></td>
</tr>
<tr>
<td>Geparsixto40 (296 Patients)</td>
<td>PMB</td>
<td>36.9%</td>
<td>p = .005</td>
</tr>
<tr>
<td></td>
<td>PMBCb</td>
<td>53.2%</td>
<td></td>
</tr>
<tr>
<td>I-Spy 2: Veliparib-Carboplatin Arm42 (116 Patients)</td>
<td>P → AC</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PVCb → AC</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>I-Spy 2: Pembrolizumab Arm43 (249 Patients)</td>
<td>P → AC</td>
<td>20%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPemb → AC</td>
<td>60%*</td>
<td>N/A</td>
</tr>
<tr>
<td>Geparsepto37 (276 Patients With Tnbc)</td>
<td>P → EC</td>
<td>26%*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nabP → EC</td>
<td>48%*</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Etna38 (219 Patients)</td>
<td>P → AC/EC/FEC</td>
<td>37.3%</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated pCR.

Abbreviations: pCR, pathologic complete response; TNBC, triple-negative breast cancer; P, paclitaxel; AC, adriamycin-cytoxan; CB, carboplatin; M, nonpegylated liposomal doxorubicin; B, bevacizumab; V, veliparib; pemb, pembrolizumab; nabP, nab-paclitaxel; EC, epirubicin-cytoxan; FEC, 5-fluorouracil, epirubicin, cytoxan; N/A, nonapplicable; NS, nonsignificant.
in the neratinib group and 87.7% (95% CI, 85.7%–89.4%) in the placebo group.

Interestingly, the majority of benefit was noted in HR-positive, HER2-positive breast cancers, though the trial was not powered to detect effects between subgroups.

**Pertuzumab**

Pertuzumab is a monoclonal antibody that targets the extracellular dimerization domain of HER2 and inhibits the ligand-dependent heterodimerization of HER2 with other family members including EGFR, HER3, and HER4. The CLEOPATRA study demonstrated significantly improved progression-free survival and OS with the addition of pertuzumab to trastuzumab and docetaxel in patients with metastatic HER2-positive breast cancer, leading to its initial approval. In the neoadjuvant setting, two phase II trials, NeoSphere and Tryphaena, evaluated the addition of pertuzumab to trastuzumab and chemotherapy in patients with HER2-positive breast cancer. Based on the promising safety and efficacy results of these two trials, as well as the significant survival benefit seen in the metastatic setting, the FDA granted accelerated approval to pertuzumab and trastuzumab for the neoadjuvant treatment of HER2-positive breast cancer.

NeoSphere is a multicenter randomized phase II trial studying the efficacy and safety of neoadjuvant pertuzumab and trastuzumab with docetaxel in early-stage HER2-positive breast cancer. A total of 417 patients were randomly assigned to one of four groups and received four cycles of the following therapy before surgery: trastuzumab plus docetaxel (arm 1), trastuzumab pertuzumab plus docetaxel (arm 2), trastuzumab plus pertuzumab (arm 3), or pertuzumab plus docetaxel (arm 4). After surgery, patients in all three groups received three cycles of identical chemotherapy with fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) followed by completion of 1 year of trastuzumab, with the exception of the third group in which four cycles of docetaxel were added before FEC. The primary endpoint of breast pCR was significantly higher in the arm that received trastuzumab, pertuzumab, and docetaxel compared with the other arms. DFS and progression-free survival were highest in patients who received both trastuzumab and pertuzumab in addition to docetaxel, 86% (95% CI, 77%–91%); however, confidence intervals were large and overlapping. pCR was more predictive of progression-free survival in patients with HR-negative breast cancer than in those with HR-positive breast cancer, 84% versus 72%, respectively.

TRYPHAENA is a phase II neoadjuvant cardiac safety trial that randomly assigned 225 patients to one of three arms: FEC followed by docetaxel, pertuzumab, and trastuzumab (trastuzumab and pertuzumab given concurrently; FEC + H + P → T + H + P; arm 1) or following FEC (FEC → T + H + P; arm 2) or trastuzumab, pertuzumab, docetaxel and carboplatin (arm 3). Though not the primary endpoint of this trial, most patients achieved a pCR, and there was no difference noted between the three arms (61.6% for arm 1, 57.3% arm 2, and 66.2% for arm 3). Three-year survival estimates for DFS were 87%, 88%, and 90% in arms 1, 2, and 3, respectively.

The Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer (APHINITY) trial randomly assigned 4,804 patients with node-positive or high-risk node-negative, HER2-positive operable breast cancer to receive either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. Across the trial population, 63% of patients had node-positive disease and 36% had HR-negative disease. Though statistically significant, the difference in invasive DFS at 3-year follow-up was modest at 94.1% in the pertuzumab group and 93.2% in the placebo group. In the cohort of patients with node-positive disease, the 3-year invasive DFS was 92% in the pertuzumab group compared with 90.2% in the placebo group (HR 0.77; 95% CI, 0.62–0.96; p = .02). In the cohort of patients with node-negative disease, the 3-year rate of invasive DFS was 97.5% in the pertuzumab group and 98.4% in the placebo group (HR 1.13; 95% CI, 0.68–1.86; p = .64). Toxicities did not differ between each group. The tests for interaction of the treatment effect were not significant for any of the patients of groups considered, including those based on nodal status and HR status.

**Trastuzumab Emtansine**

Trastuzumab emtansine (T-DM1) is a novel antibody-drug conjugate that links trastuzumab with a cytotoxic antimicrotubule agent, DM1, a maytansine derivative. T-DM1 is approved as second-line therapy for metastatic HER2-positive breast cancer, based on the results of the EMILIA trial. The large multicenter randomized phase II-III umbrella trial ADAPT (Adjuvant Dynamic Marker-Adjusted Personalized Therapy trial) is designed to enroll approximately 5,000 patients into four distinct subtrials based on breast cancer subtype. In one of the subtrials, patients with HER2-positive, HR-positive breast cancer were randomly assigned to receive 12 weeks of T-DM1 alone, T-DM1 plus endocrine therapy, or trastuzumab plus endocrine therapy. The study was closed early after 376 of the planned 380 patients were enrolled as a result of the efficacy endpoint of pCR having been reached after the first interim analysis. The arms containing TDM-1 achieved higher pCR rates: 40.5%, 45.8%, and 6.7% for T-DM1 alone, T-DM1 plus endocrine therapy, and trastuzumab plus endocrine therapy, respectively. The addition of endocrine therapy to T-DM1 did not increase pCR. Interestingly, early response biomarkers, including low cellularity or decreased Ki-67 of greater than 30% were significantly associated with a higher pCR. Several other neoadjuvant trials of T-DM1 are ongoing and listed in Table 3.

In summary, trials to date show that the addition of lapatinib and pertuzumab to trastuzumab, or the substitution of neratinib for trastuzumab, increase pCR rates compared with trastuzumab alone. However, these increases in pCR have not improved longer-term outcomes consistently and across all subgroups. Patients who do achieve a pCR have superior outcomes compared with those that do not. Therefore, the neoadjuvant setting using pCR as an endpoint remains a useful tool for the evaluation of new agents and/or the de-escalation of therapy in the HER2-positive setting.
**CONCLUSION**

Depending on breast cancer subtype, the neoadjuvant setting allows a rapid, cost-effective means of evaluating novel therapeutic approaches in patients with early-stage breast cancer. PCR is a reasonable surrogate endpoint for patients with TNBC and HER2-positive breast cancers, and it has been consistently shown to be associated with improved outcomes. In patients with HR-positive breast cancer, the use of pCR as an endpoint is less useful, and other endpoints, such as changes in Ki-67, may be more reasonable.

**References**


Intratumor gene\textsuperscript{o}c heterogeneity refers to the coexistence of genetically distinct but clonally related cancer cells within the same patient. It can manifest itself as distinct tumor cell clones in different regions of the same tumor mass (i.e., spatial heterogeneity) or as genetic differences between different metastatic sites and the primary tumor from the same patient (i.e., within-patient temporal heterogeneity). Clinicians and patients have long been aware that different metastatic lesions could respond differently to the same treatment, implying clinically important phenotypic heterogeneity. The broad availability of next-generation sequencing (NGS) technologies that allow rapid sequencing from a few hundred genes to the entire genome generated new insights into genomic tumor heterogeneity. Genomic heterogeneity can be studied at the single cell level by using single cell sequencing, at the level of a few dozen to a few hundred genes by using targeted sequencing, or at the level of the entire exome or genome by using whole-exome sequencing (WGS). Single-cell DNA or RNA sequencing is the most direct measure of cellular heterogeneity; however, it is limited by low and uneven coverage of the targeted regions that must be considered when cell-to-cell comparisons are performed. It has potential to teach us about cellular dynamics in a tumor mass but currently has no immediate clinical utility.

Targeted sequencing of genes of interest can provide very high target coverage to reliably identify mutations and estimate the mutation frequency (i.e., variant allele frequency) in DNA extracted from tissue. The FoundationOne assay (Foundation Medicine, Cambridge, MA), the Oncomine test (ThermoFisher Scientific, Waltham, MA), and the numerous sequencing panels in clinical molecular pathology laboratories are examples of targeted sequencing. Results from these assays have important clinical utility in selecting patients for therapy when drug efficacy depends on the mutation status of a gene. A typical cancer harbors thousands of germline single-nucleotide variants that might alter protein function (based on mathematical models) and few dozens to a several hundreds of somatic variants as well as numerous large-scale structural alterations in the genome. Clinical and biologic interpretation of the net effect of all these abnormalities remains a challenge. These methods, when applied to multiple tumor tissues from the same patient, or to pre- and post-treatment samples, also allow reconstruction of clonal evolution and the tumor’s evolutionary path.

Understanding tumor heterogeneity and clonal selection dynamics is important for three conceptual reasons. First, genomic measures of overall tumor clonal heterogeneity may provide prognostic or predictive information. Several methods exist to quantify clonal composition and heterogeneity based on clustering of variant (i.e., mutant) allele frequencies (VAFs; PyClone\textsuperscript{1} SciClone\textsuperscript{2} and THetA\textsuperscript{3}) or measuring the variance of the VAF frequency distribution (MATH score\textsuperscript{4}). These metrics indicate that intratumor genetic heterogeneity is greater in breast cancer among African American patients\textsuperscript{5} and that greater tumor heterogeneity tends to be associated with worse prognosis.\textsuperscript{6} In triple-negative
breast cancer (TNBC), greater clonal mutation burden is also associated with greater chemotherapy sensitivity.7

Second, the evolutionary relatedness of metastatic lesions and the primary tumor can help reconstruct the metastatic process. It has been long suspected, but genomic studies have proven that metastatic lesions can give rise to new metastasis.8 These findings explain how postoperative radiation therapy to lymph node–bearing regions not only reduces the risk for local recurrence in the radiated field but also reduces the risk for distant recurrence. It also provides the rationale to aggressively treat oligometastatic recurrences with multimodality therapy. The impact of this approach on survival is being tested in an important ongoing clinical trial (NRG-BR002; NCT02364557).

Third, the clonal evolution of cancer under therapeutic pressure can reveal mechanisms of drug resistance. Serial tumor biopsies during treatment and, more recently, serial sampling of cell-free DNA (cfDNA) shed by tumor cells into the circulation (also known as circulating tumor DNA) may provide insights into what genomic features enable a cell clone to survive and can suggest novel therapeutic strategies. The emergence of estrogen receptor mutations that provide insights into what genomic features enable a cell clone to survive and can suggest novel therapeutic strategies. The emergence of estrogen receptor mutations that lead to hormone independent signaling during adjuvant endocrine therapy represents a clinically important example.9

HOW DOES THE PRACTICING ONCOLOGIST MAKE SENSE OF A GENOMIC REPORT?

With the advent of pan-cancer therapies, NGS has increasing clinical impact yet also poses new challenges.10,11 Although primary focus is on predicting treatment benefit, NGS also can facilitate pathologic diagnosis and prognosis and identify germline alterations that confer cancer risk. As opposed to quantitative RNA measurements, such as Oncotype DX (Genomic Health, Redwood City, CA), MammaPrint (Agenda, Irvine, CA), and PAM50 (Nanostring Technologies, Seattle, WA), NGS determines the presence/absence of genetic alterations in binary fashion and allows detection even when samples have a small fraction of tumor cells.12-14

NGS challenges the ability of oncologists to routinely and efficiently interpret genomic findings and apply these in the clinic.

Selecting a Test

Distinct molecular NGS tests are selected for a particular application with a tradeoff between breadth of coverage and sequencing depth (Fig. 1A). Depth is the number of sequencing reads of any particular region of the genome (e.g., sequencing depth of 10 is illustrated for PIK3CA in Fig. 1B). Research applications often use WGS or WES. For a given number of sequencing reads (governed by cost), WGS (Fig. 1A, blue) optimizes breadth and sacrifices depth. By contrast, WES restricts focus to the approximately 20,400 protein-coding genes, or 2% of the genome (Fig. 1A, orange). WGS and WES can be used to discover new genes or noncoding regions that regulate cancer biology. However, many of these genes are known, allowing for more focused testing of panels targeted at these genes (Fig. 1A, green). Targeted NGS provides high sequencing depth—numerous reads of the same region of the genome—to compensate for the presence of nontumor DNA in the sample. This high depth allows for robust detection of alterations hundreds of bases for samples even when tumor cells comprise 20% or less of the sample. For these reasons, targeted panels are commonly used for routine clinical applications.

The VAF is sometimes reported and can be helpful—with limitations—in adjudicating the type of mutation. For example, consider five cells in a tumor sample with 40% cancer cells and 60% noncancer cells (Fig. 1B), with each copy of DNA present in the cell read once (thus a total of two to four reads from cancer [Fig. 1B, dark] and six noncancer reads [Fig. 1B, gray]). The relevant chromosomes for these genes are illustrated in the middle panels with tumor dark, non-tumor stroma light, and the mutation site illustrated in red (versus green for no mutation). A heterozygous activating mutation of PIK3CA is expected to yield a VAF of 20%. By contrast, TP53 typically has a mutation of one allele and loss of heterozygosity in the second, as shown by the missing short arm of chromosome 17. This results in only eight reads from five cells, with two of eight harboring the TP53 mutation for an expected VAF of 25%. For a germline mutation, such as BRCA2, VAF is higher because of the presence of the mutation in the nontumor stromal cells. For mutations that appear in other compartments—such as contaminating blood cells—VAF is expected to be very low. Thus, the VAF can be informative regarding the origin and type of alteration. Yet there is typically a large error in VAF estimates relative to that expected arising for numerous reasons, including inaccurate estimates of the normal cell-to-tumor cell ratio and copy number alterations at the location of a variant allele in the cancer.15 Thus, it is important to regard interpretations of VAF as estimates rather than precise numbers.

More recently, commercial cfDNA testing has become available.16 cfDNA samples are drawn from circulating serum containing tumor DNA, apparently from spontaneously

PRACTICAL APPLICATIONS

- Genomic sequencing can provide important information about tumor heterogeneity and clonal dynamics.
- Measures of clonal heterogeneity are relevant for prognostication or prediction of benefit from treatment, understanding the metastatic process, and identifying mechanisms of treatment resistance.
- Targeted panel genomic tests on tumor are robust to small tumor fraction and are currently most relevant to routine clinical practice.
- Variant allele fraction can hint at heterozygosity and whether the mutation is present in germline.
- Patients with advanced breast cancer who have recurrent genomic alterations detected by targeted panel tests—such as ERBB2, PIK3CA, AKT1, and ESR1 mutations; NTRK fusions; dMMR; or high tumor mutational burden—should be considered for early referral for clinical trials.
lysed tumor cells. Validated cfDNA assays show high, but not perfect, concordance with that of primary tumor. The clinical implications of discordant results are yet to be clarified. A potential, but not yet proven, advantage of cfDNA is that it captures DNA from multiple tumor sites and may provide a more comprehensive measure of the tumor mutation profile than a single tissue biopsy.

Emerging clinical applications of cfDNA in breast cancer include monitoring response to neoadjuvant therapy, detecting ESR1 resistance mutations, and BRCA1/2 mutation profiling to guide utility of PARP inhibition. Ongoing studies, such as plasmaMATCH, aim to determine validity of cfDNA to predict benefit of molecular-targeted therapies. Other applications under investigation include early detection of disease recurrence and classification of tumor heterogeneity. However, cfDNA testing may be less sensitive than tumor profiling, especially for patients with low metastatic burden. cfDNA is considered when tumor samples are not readily accessible or in detecting secondary mutations that arise after targeted therapy, such as ESR1 mutations after endocrine therapy or reversion mutations in BRCA1 after PARP inhibitor treatment.

**Interpreting Results**

Clinical NGS reports typically list presumed driver alterations with the resulting changes in the protein code. Common single-site alterations are typically reported as mutations of the protein, such as ESR1 p.Y537S, a mutation leading to change from tyrosine (Y) to serine (S) at the 537th amino acid position on the protein encoded by estrogen receptor α gene. However, the same genomic alteration could also be reported at the DNA sequence level as c.1610A>C, indicating a nucleic acid change from adenine (A) to cytosine (C). More complex alterations affect multiple amino acids. For example, EGFR L747_A750del indicates a deletion of 12 nucleotides from exon 19 of the EGFR gene, resulting in removal of four amino acids, 747–750, where L and A correspond to leucine and alanine at the given locations. Mutations in single amino acids or small deletions can either activate or inactivate a protein.

By contrast, inactivation is the typical result of mutations that cause mis-splicing or frameshift/truncation. Frameshifts occur by insertion and/or deletion (“indel”) of nucleotides in units other than multiples of three. These alter protein translation to the wrong reading frame and typically result in coding a small number of erroneous amino acids followed by a stop codon. Frameshifts are typically reported as fs*N, where N is the number of erroneous amino acids encoded prior to a premature stop codon. For example, BRCA2 P447fs*13 indicates a frameshift mutation that encode 13 additional erroneous amino acids and a stop after proline at amino acid position 447 in the protein sequence and is expected to yield a nonfunctional truncated protein (BRCA2 normally has 3,418 amino acids). Splice-site alterations are mutations in noncoding regions in introns near the boundary of the exons that result in removal of an exon, typically leading to a nonfunctional protein. As a whole, NGS is optimal for reading these small mutations, indels, and splice-site mutations.

Larger genetic aberrations can cause amplification and deletions of entire genes or chromosomal regions encompassing many genes. Larger alterations reported include amplifications/deletions and fusions. Amplifications and deletions are reported when specific genomic regions are detected in greater/fewer NGS reads than expected by chance. These can be helpful, for example, in detecting ERBB2 (HER2) amplification, which can then be verified by a validated ASCO/College of American Pathologists assay. However, not all amplified genes drive tumor growth. For example, we have often detected coamplification of FGF3, FGF4, and FGF19, all of which map to the long arm of chromosome 11 (11q13), indicating amplification of an entire genomic region, rather than a specific driver gene. Finally, many assays are designed to detect specific fusion genes that drive growth of cancer. Typically assays use extracted RNA to identify fusions, such as

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**FIGURE 1. Understanding Molecular Profiling**

A. Exome

B. Tumor Fraction 40%

- PIK3CA
  - Tumor: 24, VAF: 20%, Interpretation: somatic, heterozygous
- TP53
  - Tumor: 32, VAF: 25%, Interpretation: somatic, loss of heterozygosity
- BRCA2
  - Tumor: 32, VAF: 62%, Interpretation: germline, loss of heterozygosity

Coverage (bp)

- 10^9
- 10^8
- 10^7
- 10^6
- 10^5

Depth

- 1
- 10
- 100
- 1000

Coverage (bp)

- 10^9
- 10^8
- 10^7
- 10^6
- 10^5

Depth

Abbreviation: VAF, variant allele frequency.
as those that activate FGFR1-3 or NTRK—detecting these in spliced RNA is more efficient than examining genomic DNA because the particular exons involved are variable. However, activating gene fusions are rare in breast cancer.

In addition to reporting these alterations, most tests are now designed to detect additional actionable findings, such as DNA mismatch repair deficiency (dMMR), which manifests as microsatellite instability. dMMR is a marker of immunotherapy benefit24 and tumor mutational burden (TMB)—the number of somatic coding base substitution and indel mutations per megabase of genome examined, including passenger mutations. TMB quantifies mutations that may make the tumor more visible to the immune system by creating non-normal peptides that are presented by major histocompatibility complex class I. However, dMMR and high TMB are rare in breast cancer.

Some pitfalls in interpreting test results are distinguishing driver and passengers and identifying the origin of the alteration. Most genomic tests will primarily report only driver mutations, those known to promote and sustain tumor growth. These are distinguished from passenger mutations that are specific to the tumor but are not known to regulate tumor growth. Most common driver alterations are well established, but uncommon alterations can be more difficult to adjudicate. It is sometimes helpful to evaluate these less common alterations through independent review of databases, such as COSMIC and cBioPortal, to visualize frequency of alterations and map them onto functional domains to evaluate effect on gene function.25,26 This can help verify that the reported mutations are potentially "actionable." Some alterations can arise from nontumor elements in the sample. For example, JAK2 mutations have been reported for tumor analyses, even though they came from infiltrating blood cells in a patient with polycythemia vera.27

Selecting Therapies
A key principle underlying treatment selection is "oncogene addiction." This means that tumors are continuously addicted to the driving growth signal from an oncogene even after the tumor appears. This concept is validated across numerous oncogenes in clinical and preclinical contexts, and we regard it as a general principle underlying selection of targeted drug therapy. On the basis of this, we would consider clinical use of investigational or off-label therapy that directly inhibits an activated oncogene found in a cancer. However, inhibition of indirect (nonmutated) targets in the same pathway, such as mammalian target of rapamycin (mTOR) inhibition due to PIK3CA mutation, is often less successful, likely because of divergence and redundancy of signaling pathways. Thus, we would generally avoid indirect "pathway inhibitors," outside of a clinical trial.

A second concept that merits mention is synthetic lethality. This concept is that single-gene defects enhance dependence on a second gene that can be targeted for treatment. Few successful examples of this exist, but most important is PARP inhibition. PARP inhibitors, such as olaparib, rely on synthetic lethality to accumulate double-strand breaks specific to tumors that lack BRCA1 or BRCA2 function.28,29 Olaparib is now U.S. Food and Drug Administration–approved for metastatic breast cancer with known germline BRCA1/2 mutations,30 and we would consider extending use of PARP inhibitors to tumors that have purely somatic alterations in BRCA1/2.

Other Impacts of NGS Testing
NGS can also affect clinical care by identifying germline mutations or clarify tumor origin. For example, current guidelines for genetic testing may not capture all individual germline alterations in BRCA1/2, or some individuals may choose not to have testing. As illustrated in Fig. 1B, tumor genomics can identify a previously unidentified germline alteration. Table 1 illustrates the somatic mutation rate as identified by WGS with corresponding germline relevance for commonly altered genes in breast cancer as pooled analysis of identical WGS14 and panel testing.31,32 BRCA1/2 mutations have a high rate of germline mutations, and, when these mutations are discovered in tumors, patients should be referred for genetic counseling. Tumor mutations at ATM, PMS2, CHEK2, ATR, and CDH1 are sometimes germline, and consultation with genetic counseling should be considered, guided by clinical and family history as a shared decision. Although hereditary syndromes are known for PTEN and TP53, somatic findings rarely reflect germline mutation. In addition to TP53 and PTEN, for most observed somatic mutations not in Table 1, matching germline alterations are exceptionally rare.

On occasion, genomic profiles can yield surprising results. For example, a patient referred to our center for a second opinion on metastatic breast cancer was found to have an EGFR exon 19 deletion, suggesting this was lung in origin and providing a therapeutic option. Because of the multiple domains of knowledge required to interpret results, it is helpful to vet these through tumor boards with experts in pathology, genetics, pharmacy, and cancer therapy. Some molecular tumor boards have begun to engage community

<table>
<thead>
<tr>
<th>Gene</th>
<th>Somatic Rate (%)</th>
<th>Germline Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA2*</td>
<td>1.96</td>
<td>4.55</td>
</tr>
<tr>
<td>BRCA1*</td>
<td>0.89</td>
<td>4.62</td>
</tr>
<tr>
<td>ATM*</td>
<td>0.36</td>
<td>0.56</td>
</tr>
<tr>
<td>PMS2**</td>
<td>0.18</td>
<td>0.19</td>
</tr>
<tr>
<td>CHEK2**</td>
<td>NA</td>
<td>0.83</td>
</tr>
<tr>
<td>ATR*</td>
<td>0.54</td>
<td>0.19</td>
</tr>
<tr>
<td>CDH1**</td>
<td>0.63</td>
<td>0.19</td>
</tr>
<tr>
<td>PTEN*</td>
<td>16.1</td>
<td>0.56</td>
</tr>
<tr>
<td>TP53†</td>
<td>41.8</td>
<td>0.28</td>
</tr>
</tbody>
</table>

*Referral to genetic counseling recommended if de novo.
**Consider referral to genetic counseling as shared decision.
†Unlikely germline, updated family history review recommended.
Abbreviation: NA, not available.
practices, which can facilitate interpretation and decision making of reports.33,34

**HOW DO MOLECULAR PANELS HELP ME MAKE CLINICAL DECISIONS ABOUT MY PATIENTS?**

Early-Phase Clinical Trial Considerations

With many available chemotherapy treatment options for metastatic breast cancer, referral for early-phase clinical trials is historically considered only when all standard treatment options have been exhausted.35 Outcomes for patients with metastatic breast cancer enrolled in early-phase clinical trials35,36 have improved, supporting earlier referral for clinical trial assessments. This is particularly relevant for patients expected to have a low response rate or limited durability of response, such as TNBC after first-line chemotherapy37 or other breast cancer subtypes with poor response to initial chemotherapy.38 Below we summarize evidence for specific molecular alterations that may be relevant for clinical trials with novel drug treatments (Table 2).

**ERBB2 Mutation**

The ERBB2 gene that encodes for the transdermal human epidermal growth factor receptor 2 (HER2) growth factor receptor is a well-credentialed genomic driver in breast cancer; drugs that target the HER2 receptor have transformed outcomes for patients with ERBB2 amplified (HER2-positive) breast cancer.39 Recurrent somatic mutations of ERBB2 are identified in 2% to 4%,40,41 most frequently in non–ERBB2-amplified (HER2-negative) breast cancers, that activate HER2 signaling and can be inhibited by irreversible HER2 tyrosine kinase inhibitors (TKIs), such as neratinib, in preclinical models.42 A phase II trial of neratinib reported a response rate of 24% and a CBR of 54% regardless of HER2 status.51 In two phase III clinical trials evaluating buparlisib plus fulvestrant in hormone- (BELLE-2)53 and everolimus- (BELLE-3)54 pretreated populations, no significant benefit was seen in PIK3CA wild-type cohorts, with grade 3/4 events occurring in 63% of the buparlisib-treated group. Comparatively, PIK3CA-mutated patients showed a 3- to 4-month improvement in survival. The α isoform–specific or α isoform–selective PI3K inhibitors (alpelisib, taselisib) have shown promising results. A phase I clinical trial of alpelisib in combination with letrozole demonstrated a CBR of 44% in PIK3CA-mutant patients, with a more favorable toxicity profile.55 The combination of ribociclib with alpelisib and letrozole demonstrated similar response rates (44%) regardless of PIK3CA mutation status.56 Taselisib, a p110α–selective, β-isoform–sparing inhibitor, has shown response rates of 36% to 38% in combination with endocrine therapy in phase I/II trials of PIK3CA-mutant patients.57,58 The phase III SOLAR-1 (alpelisib; NCT02437318) and SANDPIPER (taselisib; NCT02340221) studies with pre-planned PIK3CA mutational analysis are under way.

**TABLE 2. Selected Genomic Alterations and Relevance for Clinical Trials With Novel Drug Therapies**

<table>
<thead>
<tr>
<th>Molecular Alteration</th>
<th>Subtype Considerations</th>
<th>Drug Class</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERBB2 Mutation</strong></td>
<td>2%–4% HER2-negative</td>
<td>HER2 TKI</td>
</tr>
<tr>
<td><strong>PIK3CA Mutation</strong></td>
<td>30%–40% ER+/HER2+, 20%–25% HER2+, 10%–15% TNBC</td>
<td>PI3-kinase inhibitor (α-isoform–specific/selective)</td>
</tr>
<tr>
<td><strong>AKT1 Mutation</strong></td>
<td>2%–5% breast cancer</td>
<td>AKT inhibitor mTOR inhibitor</td>
</tr>
<tr>
<td><strong>ESR1 Mutation</strong></td>
<td>30%–40% ER+/HER2+ after AI</td>
<td>Oral selective estrogen receptor degrader</td>
</tr>
<tr>
<td><strong>NTRK Fusion</strong></td>
<td>Enriched in secretory (TNBC)</td>
<td>TRK inhibitor</td>
</tr>
<tr>
<td><strong>High Tumor Mutation Burden</strong></td>
<td>1%–5% breast cancers</td>
<td>Immune checkpoint inhibitor</td>
</tr>
<tr>
<td><strong>Mismatch Repair Deficiency Signature</strong></td>
<td>&lt; 5% breast cancers</td>
<td>Immune checkpoint inhibitor</td>
</tr>
</tbody>
</table>

Abbreviations: TKI, tyrosine kinase inhibitor; ER, estrogen receptor; TNBC, triple-negative breast cancer; AI, aromatase inhibitor.
**AKT1 Mutation**
The AKT protein kinases (AKT1/AKT2/AKT3) are key downstream effectors of the PI3-kinase pathway. AKT1 is mutated in 2% to 5% of breast cancers and may be enriched in patients with ER+/HER2− metastatic disease. More than 90% of mutations in AKT1 occur at a single locus (E17K) that causes AKT1 localization to the cell membrane and constitutive signaling activity. In part D of a phase I trial, the oral pan-AKT inhibitor AZD5363 produced responses in 20% (4 of 20) ER+/HER2− patients treated with monotherapy with a median progression-free survival of 5.5 months. Responses were also observed in two patients with TNBC (out of six response-evaluable patients). Persistent declines in cfDNA AKT1E17K levels were associated with prolonged response to therapy. The combination of fulvestrant and AZD5363 in patients with AKT1 E17K mutant ER+/HER2− breast cancer recently reported a response rate of 26% with a CBR of 39%. In the SAFIR-01 trial, three of six patients with AKT1-mutant breast cancer responded to mTOR inhibitors, but additional data are needed to confirm whether AKT1 mutation sensitizes to downstream pathway inhibition.

**ESR1 Alterations**
Mutations in the estrogen receptor (ESR1) gene are infrequent in primary ER-positive breast cancer. Activating ESR1 gene mutations or fusions can be detected in tumor samples or cfDNA from patients with metastatic ER-positive breast cancer that confer ligand-independent activation and resistance to aromatase inhibitor therapy. Clinical dosing of fulvestrant, a selective estrogen receptor modulator, is limited by its highly lipophilic formulation for intramuscular injection rather than plasma exposure-mediated toxicity. No differential clinical activity for fulvestrant is observed on the basis of cfDNA ESR1 mutation status. Oral selective estrogen receptor degraders are a novel class of endocrine agents in clinical development that demonstrate preclinical activity in ESR1 wild type and mutant breast cancer models, albeit with higher drug concentrations required to inhibit ESR1 mutant models. Responses and/or prolonged disease control have been reported in ongoing trials with oral SERDs, such as GDC-0810, elacestrant (RAD1901), LSZ102, and GDC-0927, including patients with ESR1 wild type and mutant ER-positive breast cancers.

**TRK Fusions**
The Trk receptor family includes three transmembrane proteins (TrkA, TrkB, and TrkC) encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively. Secretory breast carcinoma is a rare subtype of TNBC that is characterized by a fusion of the *ETV6-NTRK3* gene that leads to ligand independent activation of the TRK kinase domain. Activating fusions that involve NTRK genes can be identified in a variety of adult and pediatric solid tumors by using NGS panel tests or fluorescent in situ hybridization. Entrectinib (RXDX-101) is an oral inhibitor of Trk kinases, as well as the C-ros oncogene (*ROS1*) and anaplastic lymphoma kinase (*ALK*). Responses were observed in three of four patients with NTRK fusions treated with entrectinib in a phase I trial, although none had breast cancer. Larotrectinib (LOXO-101) is an oral selective Trk kinase inhibitor that recently reported a 76% response rate in patients with NTRK fusions across 17 tumor types in a phase I trial. This initial report included a 14-year-old patient with chemotherapy-refractory secretory breast carcinoma treated on an expanded-access program who had a dramatic chest wall response to larotrectinib.

**Immune Biomarkers**
Immune checkpoint inhibition is effective for hematologic and solid tumor malignancies, but identification of predictive biomarkers has been difficult. PD-L1 is expressed in TNBC and other subtypes, but variable testing methods and definition(s) of positivity have made comparison difficult. Aggregate genomic biomarkers, such as high TMB, or dMMR have also shown response correlates in other cancers. In a sentinel paper by Alexandrov and colleagues, identification of 21 mutational signatures from more than 7,000 human cancer(s) with WGS using base-substitution (ie: C > G) profiling, revealed two signatures (2,13) in breast cancer associated with high TMB (> 20 mutations/megabase) and the apo-lipoprotein B messenger RNA–editing enzyme, catalytic polypeptide-like (APOBEC) family of cytidine deaminases. These enzymes possess a mutagenic role in the development of localized hypermutated regions of DNA (kataegis). Evaluation of 560 breast cancer WGS confirmed an association between APOBEC (2,13) and dMMR (6, 20, 26) signatures and high TMB. However, dMMR in breast cancer is rare (< 5%), APOBEC signatures are identified approximately 20% to 30%, albeit not all with high TMB. Unlike other tumor types, such as colorectal cancer and non–small cell lung cancer, where dMMR and colorectal cancer are associated with increased responsiveness to immune checkpoint inhibition therapy, there is no clinical data for these genomic biomarkers and activity in breast cancer.

**FUTURE DIRECTIONS**
An increasing variety of genomic tests are available at the point of care that can provide important biologic insights into tumor heterogeneity. ASCO practice guidelines do not recommend genomic testing of tumors in routine practice because of limited evidence of clinical utility to guide selection of systemic therapy for patients with advanced breast cancer. Genomic testing results may be relevant to determine eligibility for clinical trials with investigational agents. This approach may be particularly relevant for patients with advanced breast cancer, for whom standard treatments are minimally effective. Further advances in sequencing technology will expand the potential clinical applications of genomic testing, including the identification of treatment-emergent clones and the detection of clinically occult minimal residual disease. Well-designed studies are needed to evaluate the clinical impact of genomic testing throughout the continuum of care for patients with advanced breast cancer.


Innovative Strategies: Targeting Subtypes in Metastatic Breast Cancer

Mark D. Pegram, MD, Yu Zong, MD, Clinton Yam, MD, Matthew P. Goetz, MD, and Stacy L. Moulder, MD

OVERVIEW

Metastatic breast cancer continues to be a life-threatening diagnosis that impacts hundreds of thousands of patients around the world. Targeted therapies are usually associated with less toxicity compared with cytotoxic chemotherapies and often induce response or durable disease control in estrogen receptor (ER) and/or HER2+ breast cancers. Drugs that target CDK 4/6 either alone or in combination with endocrine therapy have demonstrated substantial improvements in progression-free survival (PFS) compared with endocrine monotherapy. Most recently, PARP inhibitors have shown longer PFS compared with physician’s choice of chemotherapy in BRCA-associated cancers, leading to the first U.S. Food and Drug Administration (FDA) approval of a targeted therapy with the potential to benefit a subgroup of patients with triple-negative breast cancer (TNBC). Finally, newer drug delivery strategies using antibody drug conjugates have also allowed a “targeted approach” to deliver moderate to extremely potent cytotoxins directly to sites of metastatic disease, with less toxicity.

Globally, breast cancer is the fifth highest cause for cancer death overall, accounting for more than 500,000 deaths annually.1 Metastatic breast cancer is the most frequent cause of cancer death in women in low-income regions of the world and second only to lung cancer in high-income regions.1 Current estimates suggest that up to 154,000 patients are living in the United States with metastatic breast cancer.2 Many patients with metastatic breast cancer are benefitting from targeted therapy to treat their disease; however, most will not achieve prolonged, durable remissions. Fortunately, novel targeted therapy strategies are currently being tested with the hopes of improving outcomes in patients with metastatic disease.

ER+ BREAST CANCER

Although endocrine therapy remains an essential therapeutic option for those women whose tumors express the ER, intrinsic or acquired resistance inevitably emerges. Therefore, preventing and/or reversing resistance to endocrine therapy remain major research focuses for patients, clinicians, and researchers.

Cancer cells commonly exhibit loss of cell cycle control, resulting in uncontrolled cell growth. Cyclin-dependent kinases (CDKs) are a group of serine/threonine kinases that have an important role in the mammalian cell cycle. They exert their functions by interaction with regulatory subunits called cyclins. In G1 or growth phase, expression of D-type cyclins is promoted by mitogenic growth factors via multiple different signaling pathways. Cyclin D-CDK 4/6 complexes phosphorylate and inactivate retinoblastoma (Rb) tumor suppressor proteins, which cause dissociation of E2F transcription factors and the regulation of genes that trigger G1-S phase progression, DNA replication, DNA damage repair, and mitosis.3-6 Rb is considered to be the guardian of the restriction point gate in the mammalian cell cycle, because it has a fundamental role in G1-S phase transition.3

In the case of ER+ breast cancer, cyclin D1 is a major ER transcriptional target. Despite diverse mechanisms of endocrine resistance, many ER+ breast cancers resistant to hormone-based therapy remain dependent on cyclin D1 and CDK 4 to drive cell proliferation.7 Whereas Rb is functional in most luminal breast cancer, in contrast, many ER− breast cancers (e.g., basal subtype of TNBC) are characterized by the loss of RB1 activity.8,10 Consequently, basal-like breast cancer cell lines are insensitive to CDK 4/6 inhibition in vitro.11

Recently, multiple studies have shown that targeting CDK 4/6 resulted in substantial improvements in clinical response and PFS in women with metastatic ER+ breast cancer. Remarkably, three new CDK 4/6 inhibitors, including palbociclib (Ibrance, PD0332991; Pfizer, New York, NY), ribociclib (Kisqali, LEE011; Novartis, Basel, Switzerland), and abemaciclib (Verzenio, LY2834219; Lilly, Indianapolis, IN), received approvals from the FDA over a 3-year period from 2015 to 2018. These approvals were based on the initial
randomized phase II study evaluating palbociclib in combination with letrozole\textsuperscript{12} and subsequent phase III studies showing that the addition of palbociclib,\textsuperscript{13} ribociclib,\textsuperscript{14} and abemaciclib in combination with aromatase inhibitors improved PFS in the first-line ER+ metastatic breast cancer setting. Additionally, FDA approval was gained based on phase III studies evaluating the combination of palbociclib and fulvestrant (the PALOMA III study) and abemaciclib plus fulvestrant (the Monarch 2 study) in patients with endocrine refractory ER+ breast cancer.\textsuperscript{15,16}

**DIFFERENCES BETWEEN CDK 4/6 INHIBITORS**

In evaluating the three CDK 4/6 inhibitors, it should be noted that the most common side effects observed in the randomized trials were neutropenia, leukopenia, and anemia. However, serious infection or febrile neutropenia was rare. Abemaciclib, in contrast, results in less neutropenia but greater incidence of diarrhea. However, diarrhea was effectively treated and/or prevented in most patients using antidiarrheal prophylaxis. In addition, thromboembolism has been reported with abemaciclib, with an incident rate of 4% to 5% in the Monarch 2 and 3 studies.\textsuperscript{16,17}

In terms of efficacy, evaluation of the phase III registration trials has demonstrated that the relative improvement in PFS comparing combination CDK 4/6i plus endocrine therapy versus endocrine therapy alone is remarkably similar comparing the three different CDK 4/6 inhibitors. However, cross-trial comparisons suggest that response rates to abemaciclib as a single agent\textsuperscript{18} or in combination with endocrine therapy\textsuperscript{16,17} were higher than those reported with palbociclib or ribociclib. These differences in response may be important in certain clinical scenarios (e.g., visceral metastases) when choosing one CDK4/6 inhibitor over another.

**ADDITIONAL MECHANISMS BY WHICH CDK 4/6 INHIBITORS EXERT THEIR ANTICANCER EFFECTS**

Although Rb proficiency is considered essential for the function of CDK 4/6 inhibitors, there may be Rb-independent mechanisms by which CDK 4/6 inhibitors exert their anticancer effects. Recently, Liu et al\textsuperscript{19} identified a novel mechanism by which CDK 4/6 inhibitors alter epithelial to mesenchymal transition (EMT) and inhibit metastases in TNBC. Liu et al\textsuperscript{19} showed that overexpression of DUB3 increased Snail levels, whereas conversely, knockdown of DUB3 decreased Snail protein levels without affecting SNAIL messenger RNA levels. Liu et al\textsuperscript{19} went on to show that CDK 4/6 phosphorylates DUB3 at Ser41, thus activating DUB3. Treatment of cells with palbociclib inhibited DUB3 activity, decreased SNAIL stability and expression, and decreased cell migration. In a xenograft model derived from patients with highly metastatic TNBC, the administration of palbociclib did not alter primary tumor growth but substantially reduced lung and liver metastases. Therefore, these data suggest that CDK 4/6 inhibitors may inhibit EMT and metastases independent of Rb.

Goel et al\textsuperscript{20} recently reported a novel mechanism by which CDK 4/6 inhibitors promote antitumor immunity through activation of tumor cell expression of endogenous retroviral elements and intracellular levels of double-stranded RNA, resulting in the production of type III interferons and tumor antigen presentation. Additionally, Goel et al\textsuperscript{20} showed that CDK 4/6 inhibitors suppress the proliferation of regulatory T cells and DNA methyltransferase 1, resulting in cytotoxic T cell–mediated clearance of tumor cells. Overall, these data suggest that CDK 4/6 inhibitors may contribute antitumor effects through modulation of the immune system.

**SELECTION OF PATIENTS FOR CDK 4/6 INHIBITORS**

Although CDK 4/6 inhibitors have shown substantial efficacy in patients with HR+, HER2 metastatic breast cancer, the use of these medicines involve additional toxicity (from both side effect and financial standpoints). Therefore, selecting when and in whom to administer a CDK 4/6 inhibitor is a topic of considerable debate. Previously reported subgroup analyses of the randomized phase III registration trials concluded that all subgroups benefit from the addition of CDK 4/6 inhibitors.\textsuperscript{13,14,17} However, the absolute benefit of CDK 4/6 inhibitor therapy may depend on the clinical scenario. For example, a recent analysis of over 1,000 patients enrolled in the Monarch 2 and 3 studies evaluated a broad set of common clinical and pathologic variables associated with the prognosis of patients receiving endocrine monotherapy. In this analysis, patients with liver metastases, high-grade tumors, PR− tumors, or a short treatment-free interval had a poor prognosis. Conversely, patients with bone-only disease, excellent performance status, or a long treatment-free interval exhibited substantially better prognosis. Although abemaciclib conferred benefit regardless of baseline characteristics, the patients with the poorest prognosis (e.g., liver metastases) derived the largest absolute benefit from the addition of abemaciclib to endocrine therapy. In contrast, in the Monarch 3 study, little if any benefit was noted for the addition of abemaciclib to endocrine therapy in women with a prolonged treatment-free interval. Although these
data are hypothesis generating, they suggest that there may exist a subset of patients with highly endocrine-sensitive breast cancer for whom endocrine monotherapy (e.g., an aromatase inhibitor or fulvestrant) may be the optimal first-line therapy followed by the addition of a CDK 4/6 inhibitor at progression. Additional clinical studies are necessary to determine the optimal strategy.

**MECHANISMS OF RESISTANCE TO CDK 4/6 INHIBITORS**

Similar to the paradigm of treating ER+ breast cancer, the mechanisms of resistance to CDK 4/6 inhibitors can be divided into de novo and acquired resistance. Currently, ER status is the only selection criteria used for women with metastatic breast cancer being considered for a CDK 4/6 inhibitor. Biologically plausible biomarkers of the cyclin D-CDK 4/6-Rb pathway (e.g., loss of Rb and consequent upregulation of p16INK4A and downregulation of cyclin D1) have not been consistently associated to the benefit of CDK 4/6 inhibitors in the randomized trials.\(^2\) For example, cyclin D1 amplification and/or loss of CDKN2A were not associated with palbociclib resistance in the PALOMA 1 study.\(^3\) Furthermore, Rb, cyclin D1, p16, and Ki-67 (all evaluated by immunohistochemistry) were not predictive of palbociclib benefit in the PALOMA 2 study.\(^4\) Although loss of RB1 function is relatively rare in newly diagnosed patients with ER+ breast cancer,\(^5\) the incidence of Rb loss, E2F amplification, and/or loss of CDKN1 and their association with acquired resistance to CDK 4/6 inhibitors are unknown.

**COMBINATION THERAPY STRATEGIES**

There is great rational for combining CDK 4/6 inhibitors with drugs that target growth factor signaling pathways upstream of cyclin D1, including drugs that target the PI3K/mTOR/AKT pathway.\(^6\) These data have resulted in several ongoing studies, in which CDK 4/6 inhibition is combined with drugs that target this pathway. Furthermore, there exists substantial rationale for the use of CDK 4/6 inhibitors in combination with HER2-directed therapy in patients with HER2-amplified breast cancers. In addition to the surprising single-agent activity of abemaciclib in ER+/HER2+ breast cancer,\(^7\) there are extensive preclinical data identifying cyclin D1 as a critical downstream target of HER-induced transformation\(^8\) and providing evidence of synergy when combining CDK 4/6 inhibitors with anti-HER2–based therapy. Based on these data, multiple clinical trials are ongoing to evaluate the combination of HER2-directed therapy and CDK 4/6 inhibitors in ER+/HER2+ breast cancer.

Finally, recent data suggest the FGFR kinase may also mediate resistance to CDK 4/6 inhibitors. Formisano et al.\(^9\) not only identified FGFR1 as associated with resistance to AI-based therapy\(^10\) but additionally, identified FGFR1 amplification as a mechanism of resistance to the combination of ribociclib and fulvestrant in vitro.\(^11\) In this report, the addition of the FGFR tyrosine kinase inhibitor erdafitinib to fulvestrant/palbociclib resulted in marked regressions in vivo. Based on these data, a clinical trial is planned to combine erdafitinib with a CDK 4/6 inhibitor in ER+ FGFR–amplified breast cancer.

**HER2+ BREAST CANCER**

A myriad of molecular mechanisms have been postulated to be associated with resistance to various HER2-targeted therapies (Fig. 1). Indeed, a comprehensive outline of humanized monoclonal anti-HER2 antibody trastuzumab resistance biomarkers in HER2-overexpressing breast cancer has been cataloged in a scholarly review by Menyhárt et al.\(^12\) Among the types of biomarkers most well studied to date are (1) perturbation of HER family receptors or binding of therapeutic antibodies to HER2 (e.g., shedding of the HER2 extracellular domain,\(^13\) expression of the Δ16HER2 splice isoform expression,\(^14\) overexpression of MUC4/MUC1 resulting in steric hindrance to trastuzumab binding to the HER2 extracellular domain,\(^15\) and increased phosphorylation of HER3\(^16\)); (2) parallel receptor pathway activation (e.g., upregulation of IGF-1 receptor,\(^17\) erythropoietin receptor,\(^18\) AXL receptor,\(^19\) or MET receptor\(^20\)); and (3) activation of downstream signaling events distal to HER2 receptor (e.g., hyperactivation of the PI3 kinase/Akt pathway by loss of PTEN or PIK3CA mutational activation,\(^21\) cyclin E amplification/overexpression,\(^22\) upregulation of mir-21,\(^23\) and expression of the ER\(^24\)). Of these and other potential resistance pathways, not all have been confirmed to occur in human clinical/translational cohorts with annotated outcomes, and even those that have at least some clinical evidence from discovery cohorts lack validation cohorts and/or independent confirmation across multiple trials. Fewer still have prospective clinical/translational efforts of new therapeutic approaches to overcome resistance to HER2-targeted therapeutics (Table 1). Herein, we discuss three resistance mechanisms addressed by recent/ongoing interventional clinical trials: (1) the use of antibody-drug conjugate (ADC) ado-trastuzuman emtansine (T-DM1) to overcome resistance as a result of PIK3CA mutation, (2) the use of novel approaches to enhance antibody-dependent cell-mediated cytotoxicity (ADCC) of immune effector cells to address resistance caused by low-affinity activating Fcγ receptor (FcγR) polymorphisms, and (3) solutions to overcome anatomic resistance by the blood-brain barrier in HER2+ brain metastasis.

**OVERCOMING RESISTANCE AS A RESULT OF PIK3CA MUTATION USING ADC T-DM1**

One of the best characterized mutational events associated with resistance to both HER2-directed monoclonal antibodies (mAbs) and small molecule HER2 kinase inhibitors is somatic mutation of the PIK3CA gene—the most common molecular alteration in human breast cancer. We hypothesized that treatment with T-DM1 would be agnostic to the presence or absence of downstream activating PIK3CA mutations, because cytotoxicity of the derivative of maytansine 1 cytotoxic payload of T-DM1 is not dependent on activation status of the PI3 kinase signaling pathway. We had the opportunity to test this hypothesis by investigating whether the efficacy of T-DM1 was correlated with PIK3CA mutation
in the phase III pivotal registrational EMILIA study—a randomized phase III study of T-DM1 versus lapatinib and capecitabine in 991 patients with metastatic HER2+ cancer who had prior treatment with trastuzumab and a taxane. Tumor tissue was collected (with additional consent) and subjected to PIK3CA DNA sequence analysis (259 patients) using the cobas PIK3CA mutation test (Roche Molecular Diagnostics) for exon 1: R88Q; exon 4: N345K; exon 7: C420R; exon 9: E542K, E545X, and Q546X; and exon 20: M1043I, H1047X, and G1049R. PFS and overall survival were analyzed using the Kaplan–Meier method and a Cox regression model. Moreover, T-DM1 was also tested on cell lines and in HER2+ breast cancer xenograft models containing defined activating PIK3CA mutations. PIK3CA mutation frequency (30.5%) was similar across both treatment arms and consistent with previously reported data. PIK3CA mutations were associated with shorter median PFS (mutant vs. wild type: 4.3 vs. 6.4 months) and overall survival (17.3 vs. 27.8 months) in patients treated with capecitabine plus lapatinib but not patients treated with T-DM1 (PFS, 10.9 vs. 9.8 months; overall survival, not yet reached in mutant or wild-type groups). Additionally, T-DM1 showed potent activity in cell lines and xenograft models with known activating PIK3CA mutations. We concluded that, despite the observation that other standard HER2-directed therapies are less effective in tumors with PIK3CA mutations, T-DM1 seems to be effective in both PIK3CA-mutated and PIK3CA wild-type tumors.

**FIGURE 1. Selected Examples of Resistance to HER2-Targeted Therapies**

IGF-1 receptor (far left) and MET (far right) are shown as two examples of parallel receptor pathway activation to bypass HER2 (downstream signaling in light blue). Truncated HER2 C-terminal fragments/isozymes resulting from proteolysis of p185HER2 (p95-HER2), alternative initiation of translation (p110-HER2), or alternative splice variation (del exon 16) lead to loss of antibody (or ADC) binding epitopes as well as hyperactivation of downstream pathways, resulting in HER2 MAb/ADC resistance (middle section). Glycosylated MUC4 or MUC1 (middle section) has been shown to sterically hinder binding of HER2 antibodies to HER2 receptor. PI3 kinase mutation, loss of PTEN, HER2 L755S mutation, and upregulation of miR-21 as well as upregulation of IRS4 result in downstream signal activation uncoupled from control at the receptor level (maroon in the middle). Upregulation of extracellular matrix and collagen II genes leads to activation of the integrin-β1/Src signaling pathway (gold in the middle right). Alteration of HER3 expression (far right) and/or NRG-1 overexpression can result in attenuated response to HER2 targeting agents. Decreased FOXO3a can result in transcriptional upregulation of the ER, leading to relative resistance to HER2-targeting agents (yellow in the bottom left); amplified cyclin E or loss of negative regulation by p27 drives the transition from G1 to S phase (light green in the bottom right). Finally, the TGFβ/SMAD3 axis and EMT can induce cell surface CD73 expression and consequent adenosine generation, leading to tumor immune escape (left in the top box).

Abbreviations: ECM, extracellular matrix; NK, natural killer; TKI, tyrosine kinase inhibitor; ER, estrogen receptor; ADC, antibody-drug conjugate.
HUMANIZED HER2 MONOCLONAL ANTIBODY RESISTANCE MEDIATED BY LOW-AFFINITY POLYMORPHISMS IN ACTIVATING FCRS

In the case of therapeutic immunoglobulin G1 isotype humanized MAbs (like trastuzumab and pertuzumab), it is not only perturbation of downstream receptor signaling that accounts for clinical efficacy in vivo but also, FcγR-dependent ADCC mediated by various immune effectors, such as macrophages and natural killer cells. ADCC occurs when the Fc portion of the tumor-bound antibody is recognized by FcγRs. In knockout mice deficient in activating FcγR genes, the antitumor effects of trastuzumab are significantly blunted. Consistent with these observations, engineered anti-HER2 antibodies with disabled Fc domains fail to induce tumor responses in vivo, despite retained HER2 binding and growth inhibition in vitro. Conversely, antitumor antibodies are 10-fold more effective in mice deficient in inhibitory FcγRs, and antitumor antibody potency is greatly increased by engineering Fc domains to bind activating FcγR with greater affinity/avidity than inhibitory Fc receptors. Moreover, studies in the metastatic and neo-adjuvant settings suggest that single-nucleotide polymorphisms in activating and decoy FcγRs (FcγR3A and FcγR2A, respectively) may be associated with differential response to trastuzumab by modulating ADCC. This question was recently explored by Gavin et al from the National Surgical Adjuvant Breast and Bowel Project (NSABP) in their analysis of polymorphisms in FcγRs in early-stage breast cancer in the NSABP B-31 adjuvant trastuzumab trial. As expected, patients with genotype FcγR3A-158V/V or FcγR3A-158V/F received greater benefit from trastuzumab (HR 0.31; 95% CI, 0.22–0.43; p < .001) than patients who were homozygous for the low-affinity allele (HR 0.71; 95% CI, 0.51–1.01; p = .05), thus confirming prior published observations in metastatic disease to an adjuvant early-stage setting.

TABLE 1. Postulated Mechanisms of Resistance to HER2-Targeted Therapies in Breast Cancer

<table>
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<th>Proposed Mechanisms for Which There Are Only Preclinical Data</th>
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<th>Mechanisms Addressed by Ongoing or Completed Therapeutic Intervention Trials</th>
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<td>MUC1/4 overexpression</td>
<td>Truncated HER2 C-terminal fragments (P95), alternatively translated (P110), or splice isoform (Δ16HER2)—HER2 TKIs; ref. 44 failed to show unique benefit of lapatinib.</td>
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<tr>
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<td>AXL receptor activation</td>
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<tr>
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<td>MiR-21 upregulation</td>
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<td>MEK/MAPK pathway activation</td>
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<td>MIR-129-Sp downregulation</td>
<td>Extracellular matrix collagen/integrin/Src upregulation</td>
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<td>Increased normal epithelial-specific 1 gene (NES1/KLK10) expression</td>
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<td>Downregulation of endogenous CDK inhibitor P27 (kip1)</td>
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<td>GDF15-mediated activation of TGFβ receptor-Src-HER2 signaling cross talk</td>
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<td>Uptregulation of ATG-12/dysregulation of autophagy</td>
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</table>

Abbreviation: TKI, tyrosine kinase inhibitor.
FC-ENGINEERED HER2 MONOCLONAL ANTIBODY MARGETUXIMAB ELICITS POTENT ADCC REACTIONS, EVEN WITH LOW-AFFINITY ACTIVATING FC RECEPTORS

It may be theoretically possible to overcome such deficits in antibody Fc domain binding to low-affinity FcγRs by engineering the Fc domain to achieve higher binding affinity to activating FcγRs (and lower binding affinity to decoy receptors). This theoretical ideal has been achieved in the case of chimeric anti-HER2 antibody margetuximab (MGAH-22), which binds with elevated affinity to both lower- and higher-affinity forms of FcγR3A. In phase I, first-in-human dose-finding studies of margetuximab, tumor reductions were observed in over one-half (18 of 23; 78%) of response-evaluable patients with breast cancer, including durable (greater than 30 weeks) responders. Ex vivo analyses of patient peripheral blood mononuclear cell samples confirmed the ability of margetuximab to support enhanced ADCC compared with trastuzumab. In addition, margetuximab was very well tolerated, with mostly grades 1 and 2 toxicities consisting of pyrexia, nausea, anemia, diarrhea, and fatigue—similar to infusion-related reactions observed with other HER2-directed therapeutic monoclonal antibodies and thus far, with no apparent increase in cardiac adverse events. Clinical development of margetuximab has proceeded to an ongoing phase III pivotal trial comparing margetuximab directly with trastuzumab in combination with salvage chemotherapy in pretreated HER2+ metastatic breast cancer (SOPHIA trial; NCT02492711).

AUGMENTING ADCC USING AGONIST ANTIBODIES DIRECTED AGAINST CD137

Another means to augment ADCC is by activation of the costimulatory receptor CD137 (4-1BB) on natural killer cells using agonist antibodies (for example, utomilumab [the proposed nonproprietary name for PF-05082566]). CD137 activation occurs both in vitro and in the peripheral blood of women with HER2-overexpressing breast cancer after trastuzumab treatment. Stimulation of trastuzumab-activated human natural killer cells with agonistic MAbs specific for CD137 euthanized breast cancer cells (including an intrinsically trastuzumab-resistant cell line) more efficiently both in vitro and in vivo in xenotransplant models of human breast cancer. The dual antibody strategy combining a tumor-targeting antibody with a second antibody that activates the host innate immune system may improve the therapeutic effects of antibodies against breast cancer and other HER2-expressing tumors. An investigator-initiated phase IB/II clinical trial of agonist CD137 antibody utomilumab in combination with trastuzumab (or T-DM1) is currently underway (NCT03364348).

OVERCOMING ANATOMIC RESISTANCE AS A RESULT OF THE BLOOD-BRAIN BARRIER: THE CENTRAL NERVOUS SYSTEM NICHE AS A SANCTUARY SITE

A final novel form of resistance is that of anatomic resistance. Consider, for example, the central nervous system (CNS) microenvironment, which consists of a unique vascular endothelium (the so-called blood-brain barrier), pericytes, astrocytes, and glial cells, all of which may contribute in concert to pathogenesis of the CNS metastatic niche. HER2+ breast cancer has a strong predilection for metastasis to the CNS, with as many as one-half of all patients with HER2+ metastatic breast cancer experiencing brain metastasis during their treatment course. CNS metastases can develop during efficacious treatment of extracranial metastasis with HER2 monoclonal antibodies, suggesting that the CNS is a sanctuary site for HER2+ cancer cells. Indeed, it is argued that the macromolecular size of monoclonal antibodies (150 kd) is a severe handicap for their diffusion in therapeutic concentrations across the blood-brain barrier. This model assumption affords the novel hypothesis that diffusion of macromolecular antibody therapeutics, such as trastuzumab, may be achieved through mass action (compare with the Le Chatelier Principle) simply by increasing the concentration of trastuzumab in the circulation (recall that trastuzumab had no defined maximum tolerable dose during dose escalation, and therefore, the dose can arguably be increased with impunity). To test this hypothesis, a trial of high-dose (6 mg/kg weekly) trastuzumab (in combination with standard dose pertuzumab for control of extracranial metastasis) for HER2+ CNS metastasis is currently ongoing (NCT02536339). Consistent with this hypothesis, previous publications have documented diffusion of positron-emitter 89ZR-conjugated trastuzumab with localization to HER2+ CNS in humans. Moreover, multiple groups have documented clinical responses to ADC T-DM1 (with molecular weight slightly higher that of trastuzumab) in HER2+ CNS metastasis.

Meanwhile, small molecule HER2 tyrosine kinase inhibitors continue to be developed as treatment of HER2+ CNS metastasis. Historically, modest results have been obtained from the combination of lapatinib with capecitabine. Newer encouraging data have recently been presented for neratinib in combination with capecitabine and highly HER2-selective tyrosine kinase inhibitor tucatinib (ONT-380)-based regimens. If pathogenic factors within the CNS metastatic niche can be identified (such as chemotactic factors, adhesion, and transendothelial tumor cell extravasation factors as well as peptide growth factors), there may be unique opportunities for exploiting novel treatment approaches or perhaps more importantly, opportunities for prophylaxis against HER2+ brain metastasis altogether.

TRIPLE NEGATIVE BREAST CANCER

TNBCs account for 10% to 20% of primary breast cancers and are so named, because they express low levels of ER, PR, and HER2. Early efforts to develop targeted therapy strategies resulted in lackluster clinical response rates in TNBC, which is now presumed to be related, in part, to molecular heterogeneity within the “catchall” diagnosis of TNBC. Recent advances in molecular characterization have shown subtypes of TNBC, each with distinct targetable molecular aberrations. Although it is anticipated that ongoing
clinical trials will lead to additional targeted therapies for TNBC, it is important to note that the only currently FDA-approved targeted therapy is olaparib for the treatment of BRCA-associated TNBC.

**BRCA-ASSOCIATED TRIPLE NEGATIVE BREAST CANCER**

*BRCA1* and *BRCA2* are required for homologous recombination repair of DNA strand breaks, leading to a defect in DNA repair in cancers harboring these mutations. As such, these tumors are more sensitive to chemotherapy-inducing DNA breaks, such as those induced by platinum-based therapies. The TNT trial randomized 376 patients with advanced TNBC to receive either carboplatin or docetaxel for six to eight cycles or until disease progression. There was no significant difference in objective response rate (ORR) or median PFS between the two arms (p = .44); however, in patients with *BRCA1/2*-associated breast cancers (43 patients), both ORR and PFS were significantly improved with carboplatin compared with docetaxel (p = .03). Notably, a diagnostic assay to measure tumor deficiencies in homologous recombination failed to predict benefit for carboplatin in non-BRCA-associated TNBC.

PARP enzymes catalyze the formation of chains of poly(adenosine 5’-diphosphate)-ribose units, which recruit the necessary DNA repair proteins. PARP inhibition leads to accumulation of single-strand DNA breaks, which lead to double-strand breaks at replication forks. In the absence of PARP, tumors that lack the ability to repair double-strand DNA breaks through homologous recombination must use less efficient mechanisms, such as nonhomologous end joining, which lead to further genomic instability and cell death. Early-phase trials of PARP inhibitors showed single-agent responses in *BRCA*-associated tumors, including in patients with TNBC. The OlympiAD trial was an open label, randomized phase III trial that compared single-agent olaparib with physician’s choice of standard chemotherapy (capecitabine, eribulin, or vinorelbine) for the treatment of *BRCA*-associated breast cancers (302 patients), one-half of which were TNBC. Median PFS was significantly longer in the olaparib group (7.0 vs. 4.2 months; HR 0.58; p < .001), and the ORR was higher (59.9% vs. 28.8%). Similar results were seen in the EMBRACA trial when the PARP inhibitor talazoparib was compared with physician’s choice of chemotherapy. However, it is important to note that neither of these trials contained a DNA-damaging agent in the “physician’s choice” arm and that both excluded patients with a history of disease progression while receiving platinum-based therapy for metastatic disease.

**IMMUNE MODULATION FOR TREATMENT OF TNBC**

Immunotherapy is a rapidly evolving strategy for the treatment of TNBC. Tumor-infiltrating lymphocytes have been recognized as a positive prognostic biomarker by analysis of data from multiple adjuvant therapy trials in unselected breast cancer. Additionally, the presence of tumor-infiltrating lymphocytes has been favorably associated with higher rates of pathologic complete response to neoadjuvant chemotherapy in TNBC. Mittendorf et al found that PD-L1 expression occurred in 20% of TNBC tumors, suggesting that targeting PD-1 or PD-L1 may have therapeutic benefit in TNBC. Currently, the most mature studies evaluating immunotherapy in TNBC involve drugs targeting the PD-1/PD-L1 axis. The KEYNOTE-012 trial was a multicenter, nonrandomized phase Ib trial of single-agent pembrolizumab (anti–PD-1) in PD-L1+ (greater than or equal to 1%) TNBC. The drug was well tolerated, with toxicities similar to those reported in other solid tumor types (low-grade arthralgia, fatigue, myalgia, and nausea). In the 27 patients evaluated for response, the overall response rate (complete response or partial response) was 18.5%, with the median duration of response not reached at the time of publication (range of 15–47+ weeks). Importantly, some responders continued treatment of over 1 year. The follow-up phase II trial (KEYNOTE-086 trial) enrolled 170 patients with previously treated TNBC and showed an overall response rate of 5%, regardless of PD-L1 expression. Median PFS and overall survival were 2.0 and 8.9 months, respectively. Similar response rates have been reported with avelumab (anti–PD-L1 antibody). The Javelin study determined the overall response rate to single-agent avelumab to be 9% in patients (58 patients) with advanced TNBC. These single-agent results suggest that combination strategies as well as novel predictors of response must be pursued to further improve clinical outcomes.

Tumor cell death induced by cytotoxic chemotherapy or radiation also has the potential to expose the immune system to higher levels of tumor antigens; thus, inhibiting PD-L1/PD-1 signaling in combination with these therapeutic modalities may theoretically result in deeper and more durable responses. Ongoing studies will determine if combining immunotherapy with chemotherapy or radiation therapy improves clinical outcomes in patients with metastatic TNBC. Preliminary safety data from the study GP28328 indicate that atezolizumab (anti–PD-L1 antibody) in combination with nab-paclitaxel and carboplatin was well tolerated, with toxiciies similar to those reported in other solid tumors (low-grade arthralgia, fatigue, myalgia, and nausea). In the 27 patients evaluated for response, the overall response rate of tumors (58 patients) with advanced TNBC was no longer identified, suggesting that this signature likely identifies immune infiltrate within stroma. Burstein et al described a basal-like immune-activated subtype that overexpressed CTLA-4 in addition to other immune-related genes. As PD-1/PD-L1 inhibitors advance as a therapeutic strategy for TNBC, it will be interesting to determine if either of these subtypes is associated with enhanced response to immunotherapy.

**PI3K/AKT PATHWAY**

The LOTUS trial investigated the benefit of administering the oral Akt inhibitor ipatasertib in combination with paclitaxel as first-line therapy in patients (124 patients) with
metastatic TNBC in a placebo-controlled, double-blind phase II trial. Median PFS was 6.2 months with ipatasertib versus 4.9 months with placebo for the entire cohort (p = .037); however, the difference in PFS was much more profound in a subgroup of tumors (42 patients) with PI3K/PI3K/AKT1/PTEN-altered tumors (9.0 vs. 4.9 months; p = .041).

Gene expression signatures have also identified breast cancer subsets enriched in EMT features. Initially, a breast cancer subset enriched in EMT was identified and named “claudin low,” because this group of tumors showed low gene expression of the tight junction proteins claudin 3, 4, and 7.117-119 Most claudin-low tumors are TNBC.117 Lehmann et al100 and Burstein et al101 also independently identified distinct subtypes of TNBC that contained gene expression profiles enriched in EMT, which they termed mesenchymal (Lehmann et al100 and Burstein et al101) and mesenchymal stem–like (Lehmann et al100). Importantly, on microdissection, the mesenchymal stem–like subtype was no longer identified in a majority of tumors tested, suggesting that this subtype call was also strongly weighted by stromal gene expression.116

Mesenchymal TNBCs carry a high rate of molecular aberrations that activate the PI3K/Akt/mTOR axis, suggesting that this subgroup may be responsive to therapeutic regimens targeting this pathway.100,117,120,121 In support of this concept, metaplastic breast cancers account for 10%-57% of TNBCs characterized as claudin low and can be clinically identified by light microscopy because of an admixture of epithelial and mesenchymal components within the tumor. These tumors are also associated with a high rate of PI3K mutations and/or activation of the PI3K pathway.121,122 Patients with metastatic, metaplastic breast cancer (52 patients) were treated in a clinical trial with liposomal doxorubicin, bevacizumab, and the mTOR inhibitor temsirolimus or everolimus (DAT or DAE).122 The ORR was 21% for DAT/DAE, and the clinical benefit rate was 43% (complete response of four, partial response of seven, and standard deviation greater than or equal to 6 months of 10). Notably, in the 43 patients who had tissue available for genomic analyses, there was a 74% incidence of activating PI3K/Akt/mTOR molecular aberrations, and this was associated with a significant improvement in ORR (31% vs. 0%; p = .04). Other therapeutic strategies with the potential to target EMT include dual PI3K/mTOR inhibitors, c-MET inhibitors, NOTCH pathway inhibitors, and TGFβ-targeted agents.

**ANTIBODIES AND ANTIBODY-DRUG CONJUGATES**

Reports of overexpression and/or enhanced EGFR signaling in TNBC125-127 led to strategies using the monoclonal anti-EGFR antibody cetuximab as a single agent or in combination with chemotherapy. Cetuximab in combination with carboplatin induced higher ORR (16%) compared with single-agent cetuximab (6%).128, however, the combination of cetuximab with cisplatin did not significantly improve ORR compared with cisplatin alone in metastatic TNBC.129 Although targeted therapy with monoclonal antibodies alone has not improved outcomes in TNBC, there is a rising interest in ADCs as a therapeutic strategy.130 ADCs allow for the select delivery of moderate to ultrapotent cytotoxic drugs by targeting tumor-associated antigens. ADC binding to these antigens induces internalization of the drug into the tumor cell and subsequent release of the “payload” cytotoxic. Promising targets for ADCs currently under development for the treatment of TNBC include trophoblast cell surface antigen, Ephrin A4, folate receptor alpha, and low-level expression of HER2.130

**CONCLUSION**

In summary, the addition of CDK 4/6 inhibitors to endocrine therapy has markedly changed the landscape of ER+ metastatic breast cancer over a short period of time. Although the available drugs show remarkable similarities in terms of PFS benefit across the FDA registration trials, differences in both toxicity and response rates have been noted, and long-term follow-up of the ongoing clinical trials will be needed to identify the optimal strategy. This includes selection of both the best initial CDK 4/6 inhibitor/endocrine therapy combination and the optimal sequence (combination vs. sequential) for patients with highly endocrine-sensitive tumors. Furthermore, additional studies to elucidate the mechanisms of resistance and biomarkers that define response/resistance to this class of drugs are needed.

HER2+ breast cancers have myriad potential resistance pathways from which to choose. Lack of real-time monitoring for emergence of resistance pathways remains a critical unmet need. To this end, new HER2-targeting therapeutic strategies must be developed to exploit our better understanding...
of resistance pathways. As an example, it has been shown that ADC T-DM1 can overcome resistance to PI3 kinase pathway activation via PIK3CA mutants. It is hoped that augmenting the immunologic mechanism of action of HER2 therapeutic monoclonal antibodies via ADCC (Fc domain antibody engineering of HER2 antibodies or activation of CD137 with agonist antibodies) may also be able to bypass other vertical or horizontal HER2 intrinsic cellular resistance mechanisms. Finally, overcoming anatomic resistance (e.g., blood-brain barrier) may be possible with high-dose trastuzumab, potent HER2-directed ADCs, or improved tyrosine kinase inhibitors with greater CNS penetration and HER2 specificity (e.g., tucatinib). It is encouraging that a number of these approaches are the focus of intense ongoing clinical investigations.

Finally, the limited success previously seen with targeted therapy in TNBC is likely the result of the molecular heterogeneity of the disease, which leads to a dilution of drug effect in unselected patients. The approval of olaparib in BRCA-associated cancers (many of which are TNBCs) shows that appropriate selection of patients for targeted therapy can be beneficial in TNBC. Through modern molecular characterization, subtypes of TNBC have emerged, and targeted strategies are being developed based on their unique features. However, subtyping by gene expression is influenced by bioinformatic methods and can have problems with reproducibility in individual patients. It is critical that these barriers be overcome to better identify patients for targeted therapy strategies.

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During the past decade, a large amount of the research effort within the field of oncology has been devoted to the development and use of targeted therapy. Great strides have been made in our understanding of which patients are appropriate candidates for certain types of treatments (immunotherapy and PARP inhibitors are good examples), and many national and international trials are under way to identify useful targeted therapies for patients with chemotherapy-resistant and/or advanced-stage disease. We have made a lot of progress, but we still have a long way to go in terms of optimizing our ability to identify targeted therapy candidates.

Understanding the past can help us shape the future, and, as we look to improve our approaches to targeted therapy across the spectrum of malignancies, the history of targeted therapy in breast cancer therapy can serve as an extremely relevant case study. Breast cancer is one of the first malignancies for which targeted therapies have been used successfully. Endocrine therapies that target the estrogen (ER) and progesterone receptor have long been the cornerstone of systemic therapy approaches for hormone receptor–positive breast cancer, and the discovery of HER2 overexpression has led to the development of multiple HER2-targeted agents that have revolutionized the way HER2-positive breast cancer is treated. Both of these targeted approaches have drastically improved outcomes for these patients. Now, with decades of successful anti-estrogen and now anti-HER2–directed therapy to build upon, our understanding of resistance to targeted therapy is becoming more nuanced. Current clinical trials in breast cancer focus on combating and preventing resistance to targeted therapy, both in the advanced stage as well as in the curative setting.

Here, we offer some insights into the history of endocrine therapy and HER2-directed therapy for breast cancer, as well as a discussion of some of the more current developments in this field. It is our hope that this perspective is helpful not only to those with a focus on breast cancer and breast disease but also for those with a broader interest in precision medicine.

ENDOCRINE THERAPY

Aiming at hormone receptors that are present on some breast cancer cells has been, essentially, the starting point of targeted anticancer therapy. In recent years, enormous research efforts have been directed at understanding and inhibiting the growth signals of cancer cells, but, in truth, the association between estrogen and breast cancer has been known since the late 19th century.1,2 The first critical observation, made by George Thomas Beatson, was that changing the hormonal environment within the patient could lead to beneficial modifications in breast tumor growth and even to regression of metastatic disease.3

Dr. Beatson, then a surgeon at Edinburgh University, developed an interest in the interaction between ovaries and breast cancer but also for those with a broader interest in precision medicine.
organisms, and Beatson took this pivotal principle to the clinic: He started to surgically remove the ovaries of patients with advanced breast cancer, and, in some of his patients, clinical improvement was seen. Without knowing about estrogen, he had discovered that its presence was crucial to the growth of some breast cancers and that removing the ovaries—the main source of estrogen—was a successful anticancer treatment.

Basically, this also is what we do today as standard of care, either by blocking estrogen on breast cancer cells (achieved by selective estrogen receptor modulators, such as tamoxifen) or by deprivation/elimination of circulating estrogen (achieved by aromatase inhibitors and ovarian suppression therapy or oophorectomy). These approaches have been the mainstay of therapy for ER-positive and progesterone receptor–positive cancers for decades and remain so today. The first modern trials of adjuvant ovarian ablation were carried out in Manchester and Norway more than half a century after Beatson’s discovery and their results were not accepted everywhere. Rather quickly, some cultural differences between Europe and the United States became apparent: in Europe, there was continuing interest in the exploitation of antihormonal approaches, whereas American researchers were more interested in the development of cytotoxic agents that could serve as the mainstay of breast cancer therapy. A bit of this trend is still present in today’s clinical practice pattern; however, globalization of research networks and information sharing has largely alleviated these historical differences.

Other interventions that indicated that hormones are important came from observations after adrenalectomy and hypophysectomy in the early 1950s; however, it took more than another decade to finally pinpoint the reason why hormonal ablation worked in some patients with breast cancer and not in others. Finally, the detection of estrogen receptors on the surface of breast cancer cells by Jensen et al in the 1960s explained why estrogen deprivation and/or receptor blockade works as therapeutic principle in many breast cancers.

**Tamoxifen**

It was not until the late 1960s that the first clinically usable anti-estrogen was discovered: Tamoxifen, a selective estrogen receptor modulator, now became an alternative to surgical removal or radiotherapeutic ablation of endocrine glands. Tamoxifen was approved in 1977 by the U.S. Food and Drug Administration (FDA) for the management of metastatic breast cancer. Interestingly, the initial studies included unselected patients because of a lack of estrogen receptor essays, but results still showed a response rate of 40% to 50% in women with advanced breast cancer. During the next decade, several clinical trials reported improvement in disease-free survival with the use of tamoxifen in both pre- and postmenopausal women with early breast cancer. By binding to the estrogen receptor on cell surfaces in a competitive manner, tamoxifen became the mainstay of endocrine intervention in all breast cancer settings and is still used today as part of the standard of care. This best-studied anticancer drug in history, with hundreds of millions of patient-treatment years, essentially marked the beginning of the era of tailored or targeted oncology. Most important, its use has led to clear-cut prolongations of patients’ lives in the advanced breast cancer setting and to important long-term benefit for patients with early-stage breast cancer.

**Aromatase Inhibitors and Ovarian Suppression**

The development of aromatase inhibitors, which, by inhibiting aromatase—the enzyme that catalyzes the conversion of androgens to estrogens—can decrease circulating estrogen to nearly zero in postmenopausal women who already lack ovarian estrogen production, was a second targeted approach that pushed the field forward. This approach became the standard of care in postmenopausal women when several pivotal studies proved it to be more effective than tamoxifen alone. More recently, it has been found that, for premenopausal women with more aggressive early-stage ER-positive breast cancer, inducing menopause either biochemically (with luteinizing hormone releasing hormone analogs such as goserelin) or surgically (with oophorectomy) followed by an aromatase inhibitor is a more effective way than use of tamoxifen alone to prevent recurrence and death as a result of breast cancer.

Combining targeted therapies, such as ovarian suppression and aromatase inhibition, can be more effective but also more toxic than using one drug alone; although the combination generally is better tolerated than cytotoxic drugs, endocrine therapies are not without adverse effects.

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**PRACTICAL APPLICATIONS**

- In the era of precision medicine, breast cancer can serve as a useful case study, because clinicians and research have decades of experience using and refining an approach to endocrine therapy and anti-HER2 therapy.
- Resistance to targeted therapy is inevitable, and learning how to prevent resistance from occurring (in the upfront setting) or how to slow it down (in the metastatic setting) has been and continues to be a focus of current research in HR-positive and/or HER2-positive breast cancer.
- New approaches to targeted therapy, when successful in the metastatic setting, have been studied in the upfront setting and often with good results.
- Financial toxicity is an issue that must be carefully considered as we weigh the risks and benefits of new drugs and new drug combinations.
- Targeted therapy is not without adverse effects and toxicities, particularly when combination therapy is used. In breast cancer, as in other specialties, we strive to better understand which groups of patients require combination therapy or more aggressive therapy and which patients can do well with less.
The importance of balance between benefit and toxicity is something that we have seen with the addition of anti-CTLA-4 and anti–PD-1 therapy in melanoma and is something that we certainly will see more of as we combine targeted therapies in other diseases. Some of the ongoing conversations about the pros and cons of more aggressive endocrine therapy in early-stage breast cancer will become important in other disease types as well. particularly as the options for combining targeted therapy move from the advanced stage to the upfront setting. Identification of patients for whom more is really more and those who can get away with less will be critically important. Patient and societal perspectives are important as we consider the substantial cost of many new medications and the lingering effects of ongoing financial toxicity on individuals and communities.

Fulvestrant

In the metastatic setting, fulvestrant is a selective estrogen receptor downregulator that not only blocks the estrogen receptor on tumor cells but also permanently degrades it, which downregulates cellular levels of ER and progesterone receptor and therefore leads to decreased cell growth in estrogen-dependent cells. It can be used alone in the metastatic setting, as can aromatase inhibitors; both can be used as part of novel combination approaches with other agents, such as mTOR or cyclin-dependent kinase (CDK) 4/6 inhibitors, these therapies will be discussed following later sections of this paper.

Endocrine treatments are important in all settings of luminal breast cancer therapy. One crucial feature for the optimal use of these agents is the identification of endocrine responsiveness, which means that proper analytic quality of receptor expression assays is critical to the successful use of endocrine therapy in the clinic. It is likely that sequential or concurrent combinations of endocrine agents with newer biologic agents will be tested and used in the future with much more detailed identification of responsiveness to specific therapies. As in other areas of oncology, improved biomarkers to better identify and eventually be able to individually select patients for given treatments on the basis of accurate prediction of response and resistance are important subjects of current and future research efforts.

ANTI-HER2 THERAPY

The first paper to identify HER2 as a proto-oncogene in human breast cancer was published in 1989. As we now know, HER2-overexpressing tumors constitute 15% to 20% of all tumors in patients with breast cancer. Since that time, there has been an explosion in our understanding of the prognostic and therapeutic implications of this oncogene, and no fewer than five drugs that target HER2 have been approved for use in the metastatic and/or (neo)adjuvant setting (Fig. 1).

Overexpression of HER2, which occurs in approximately 20% of breast cancers and largely is because of a specific gene copy number amplification, results in a hyperproliferative cancer cell and poor prognosis. This, plus emerging evidence that cancer cells can become oncogenically addicted— which means that a single aberrant oncogene becomes such a driving force for growth and proliferation that other usually relevant pathways atrophy—makes HER2 a highly attractive therapeutic target. This principle of oncogene addiction as it pertains to HER2 was supported by the finding that ongoing treatment with the anti-HER2 antibody trastuzumab added to capecitabine after disease progression on trastuzumab improved overall survival compared with change to capecitabine alone. This oncogene addiction is the basis for the practice of ongoing HER2 targeting after disease progression.

Trastuzumab

The first anti-HER2 drug, trastuzumab, is a humanized monoclonal antibody directed at the extracellular domain of the transmembrane receptor HER2. This engineered murine-derived antibody was, at the time, a highly innovative approach to therapy. Early-phase studies in advanced “HER2-positive” breast cancer (quotations marks reflect the limitation that early assays for HER2 were less accurate than they are now) revealed long-term progression-free survivors. This became known among patient advocacy groups and resulted in a blessedly short-lived controversy about compassionate-use trastuzumab as the drug underwent regulatory approval. Recent advances include validation of subcutaneously injected and biosimilar drugs that expand accessibility and availability of the drug.

Metastatic setting. On the basis of a seminal phase III trial of trastuzumab added to different chemotherapy backbones...
that revealed great improvement in progression-free survival (PFS) and overall survival despite considerable crossover. Trastuzumab was approved by the FDA in 1998 for use in combination with a taxane. The other arm of this trial that combined trastuzumab with doxorubicin/cyclophosphamide experienced an unacceptably high (27%) risk of clinical cardiotoxicity. This cardiotoxicity risk has not been replicated in several (neo)adjuvant trials that allowed concurrent use of trastuzumab with anthracycline and may have reflected the pretreated nature of the patients; however, this risk remains a consideration in combination therapy. Subsequent trials established that trastuzumab could be safely and effectively combined with a number of chemotherapy partners, including vinca alkaloids, platinum salts, and alkylators. Among the subset of dual hormone receptor–positive and HER2-positive cancers, a phase III trial of aromatase inhibition with or without trastuzumab found that these patients did very poorly on antiestrogen alone: PFS was approximately 2 months and was doubled by the addition of trastuzumab. Today, trastuzumab is incorporated with chemotherapy or antiestrogens in the first-line setting and, generally, is re-incorporated later with other backbones, after ado-trastuzumab emtansine (T-DM1) or lapatinib-containing regimens.

(Neo)adjuvant setting. The first adjuvant trials of trastuzumab in HER2-positive breast cancer were reported simultaneously at a special session during the 2005 ASCO Annual Meeting and demonstrated a relapse-free survival advantage when combined in an anthracycline/taxane-based regimen (called AC-TH) in the joint analysis of NCCTG N9831 and NSABP B-31 results and when added after chemotherapy in results from the European study HERA. These reports, which were met with a standing ovation (perhaps a first in ASCO Annual Meeting history), set the standard for incorporation of trastuzumab into treatment of early HER2-positive breast cancer, and they were confirmed and extended by the BCIRG006 trial, which also found improved outcomes when trastuzumab was added to docetaxel plus carboplatin (called TCH). Recent updates suggest that trastuzumab added to polycytotoxic chemotherapy results in a 40% proportional and nearly 10% absolute overall survival advantage. Because of the aggressiveness of all of these regimens, a simpler regimen of single-agent taxane for 12 weeks with trastuzumab for 1 year (called TH) was tested in a single-arm trial in patients with low clinical risk and HER2-positive disease; results demonstrated a 98% distant disease–free survival at 3 to 4 years and established TH as an acceptable regimen for stage I disease, especially if tumors were HR positive. In all of these trials, trastuzumab was given for 1 year; trials of shorter durations have had mixed results. As a result of these studies, trastuzumab now is incorporated into all neoadjuvant and adjuvant regimens for HER2-positive disease and is given for 1 year.

Lapatinib

Lapatinib is a small-molecule HER1/HER2 dual inhibitor. Studies suggest that the clinical effect is driven primarily by its HER2 effect.

Metastatic setting. Lapatinib was approved after a phase III trial in which was added to capecitabine (as a regimen called XL) in metastatic trastuzumab-pretreated HER2-positive breast cancer; results revealed a 50% improvement in PFS. Later studies of lapatinib added to taxanes in the earlier-line setting also suggested improvement in outcome; however gastrointestinal toxicity, particularly diarrhea, and pharmacokinetic interaction with paclitaxel required dose reduction and made lapatinib a less compelling option in the first-line metastatic setting. In heavily pretreated patients, lapatinib added to trastuzumab demonstrated improved survival compared with trastuzumab alone. Added to aromatase inhibitor in dual HR–positive, HER2-positive breast cancer, lapatinib, like trastuzumab, doubled the baseline, poor, PFS seen with aromatase inhibitors alone. With the development of T-DM1 (discussed later in the paper), XL and lapatinib plus trastuzumab have become third-line or later regimens but remain reasonable to use.

(Neo)adjuvant setting. Lapatinib in the adjuvant setting looked promising on the basis of a neoadjuvant study that demonstrated greatly augmented pathologic complete response compared with chemotherapy plus trastuzumab alone. However, other studies found a more modest impact on pathologic complete response, and a large adjuvant trial, ALTTO, failed to meet its prespecified statistical endpoint, although a numeric hazard ratio advantage of 0.84 in favor of lapatinib-containing arms was seen. Therefore, lapatinib is not included in neoadjuvant or adjuvant regimens today.

Pertuzumab

Pertuzumab is another anti-HER2 monoclonal antibody, but, unlike trastuzumab, it binds to the heterodimerization domain. Interestingly, pertuzumab adverse effects include diarrhea and rash, neither of which typically are associated with trastuzumab.

Metastatic setting. Added to trastuzumab plus a taxane in the first-line setting in the CLEOPATRA trial, pertuzumab improved both PFS and overall survival, the latter by an astounding duration: 16 months. This established a new standard for first-line therapy. The benefit of pertuzumab added to trastuzumab with antiestrogens (called THP) also was demonstrated in the PERTAIN study, in which pertuzumab added 3 months of PFS (HR 0.65) to that of an aromatase inhibitor plus trastuzumab alone. Therefore, on the basis of its large survival benefit, THP is an accepted standard of care for first-line therapy. Although it is reasonable to consider pertuzumab added to an aromatase inhibitor plus trastuzumab for first-line treatment, it lacks an overall survival advantage, so most clinicians reserve pertuzumab use for THP; unlike trastuzumab, there are no data for pertuzumab use after progression.

(Neo)adjuvant setting. Results of a single large neoadjuvant trial, NeoSPHERE demonstrated that pertuzumab added to chemotherapy plus trastuzumab significantly increased pathologic complete response; as a result, the FDA for
the first time in 2013 approved a drug on the basis of the pathologic complete response intermediate endpoint. This approach was validated by the results of the APHINITY adjuvant trial, in which event-free survival as an endpoint was improved by the addition of pertuzumab to AC-TH (AC-THP) or to the nonanthracycline TCH regimen (called TCHP),\(^{53}\) which resulted in approval by the FDA for this indication in 2017. However, it should be noted that the absolute benefit was small (HR 0.81; numerically similar to ALTTO but statistically significant), translated to a 1.6% absolute benefit in recurrence, and is without a known impact on overall survival; however, those analyses are premature. Many clinicians have interpreted the results as supportive of added pertuzumab in high-risk settings (i.e., hormone receptor-negative, node-positive disease). Therefore, pertuzumab may be incorporated into neoadjuvant or adjuvant high-risk settings and given for 1 year concurrent with trastuzumab. The benefit is far less clear in stage I/II disease. Many investigators who consider de-escalation trials are favoring trastuzumab plus pertuzumab regimens with minimizing chemotherapy; however, these regimens remain unproven.

**T-DM1**

The antibody-drug conjugate T-DM1 links the tubulin inhibitor emtansine to trastuzumab, which functionally creates a Trojan horse anti-HER2 that spares the toxicity of the free cytotoxic, which is delivered intracellularly to HER2-overexpressing cells. It can produce diarrhea and thrombocytopenia, among other adverse effects, but generally is well tolerated.

**Metastatic Setting**

In the EMILIA trial in pretreated patients with HER2-positive metastatic breast cancer, T-DM1 alone was compared with capecitabine plus lapatinib, the accepted second-line regimen at the time, and proved superior from an efficacy standpoint; results showed a nearly 6-month improvement in overall survival as well as better tolerability: 16% fewer patients suffered from severe adverse events.\(^{54}\) In the first-line setting, the MARIANNE trial found that T-DM1 and T-DM1 plus pertuzumab were no better than a taxane plus trastuzumab\(^ {55}\); by inference, T-DM1 is inferior to the standard first-line metastatic regimen TPH but remains a favored second-line regimen. T-DM1 is now standard second-line therapy in countries where it is affordable and available, and it is given alone.

**Future Directions**

Despite these advances in the management of HR-positive and HER2-overexpressing tumors, relapse and the development of metastatic disease are still very real problems, and the final common pathway for patients with HR-positive and HER2-positive metastatic breast cancer is the development of resistance to targeted treatments and continued progression of disease. The resistance to endocrine therapy or anti-HER2 therapy can be either intrinsic (de novo) resistance, wherein the tumor never responds to endocrine/anti-HER2 therapy, or—more often—acquired resistance, in which the response wanes over time and the cancer eventually progresses.\(^ {56}\) As of now, there is no known role for T-DM1 in the early breast cancer setting.

**Neratinib.** This is one of a class of irreversible HER1/HER2 small molecule inhibitors that has been in development for several years; in this case, the drug was developed over time by multiple drug companies. Although toxicity is an important issue—diarrhea predominates—central nervous system penetration is one of the areas of interest for this class.

**Metastatic setting.** In the NEFERT-T first-line trial, neratinib plus paclitaxel showed efficacy similar to that of trastuzumab plus paclitaxel,\(^ {57}\) which suggests inferiority to the standard TPH first-line regimen. Central nervous system progression appeared less frequent and occurred later in the neratinib arm of NEFERT-T; however, a Translational Breast Cancer Research Consortium (TBCRC) phase II trial of single-agent neratinib in progressive central nervous system metastases in HER2-positive disease found an only 8% response rate.\(^ {58}\) The role of neratinib at this time in the metastatic setting is unclear; additional studies are needed.

**Neo**-adjuvant setting. In the ISPY2 adaptive randomization neoadjuvant series, neratinib was compared with trastuzumab combined with a taxane and then followed by AC, and there was a suggestion of superiority in the HER2-positive cohort, especially those patients whose disease was hormone receptor negative; by ISPY2 design, this is suggestive but not definitive. More compelling evidence comes from the adjuvant ExteNET trial, in which women were randomly assigned to receive neratinib versus placebo after completion of the year of trastuzumab. This trial at 5 years revealed 27% fewer invasive disease-free survival events (absolute difference, 2.5%); however, without aggressive prophylaxis, approximately 40% of patients suffered grade 3 diarrhea.\(^ {60}\) It should be noted that the adjuvant HERA trial of trastuzumab versus nothing\(^ {61}\) examined 2 years versus 1 year of treatment without finding a difference in outcome. In ExteNET, this benefit somewhat surprisingly appeared to be driven largely by the HR-positive and node-positive (especially ≥ four nodes) subsets. On the basis of these findings, the FDA neratinib for adjuvant use in 2017. Many clinicians are still struggling to interpret and apply these findings in clinical care; most consider neratinib in high-risk node-positive settings, especially if the cancer also is HR positive.
RESISTANCE TO TARGETED THERAPY IN HR-POSITIVE BREAST CANCER

An endocrine-sensitive cell depends on the ER to internalize estrogen and transport it to the nucleus to allow for cellular proliferation. In the setting of endocrine resistance, other pathways are activated, which allows the cell to proliferate despite appropriate ER blockade (tamoxifen) or lack of estrogen (aromatase inhibitors). Several biologic mechanisms of resistance have been postulated, including ER pathway alterations (loss of ER expression, \( ESR1 \) mutation), cell cycle machinery (loss of \( Rb \) gene, p16 and p18 alteration), upregulation of alternate pathways (EGFR, HER2, PI3K, and mitogen-activated protein kinase overexpression), and changes in the apoptosis mechanisms and tumor microenvironment. Dual targeting may be important to prevent cancer cell proliferation in this setting.

CDK 4/6 inhibitors

The CDK inhibitor story is perhaps one of the most important targeted therapy stories of the past few years. Scientists discovered that \( Rb \) phosphorylation by CDK 4/6 promotes the G1-to-S phase transition and that this pathway may be upregulated in endocrine-resistant cells. If CDK 4/6 could be blocked and control over the cell cycle could be regained, perhaps cancer cells would remain sensitive to endocrine therapy. PALOMA-1 (NCT02614794), the first randomized trial of CDK 4/6 inhibition in breast cancer, was a phase II study to evaluate letrozole plus palbociclib, a CDK 4/6 inhibitor, versus letrozole alone as first-line therapy for metastatic ER-positive breast cancer. Extraordinarily, the PFS was 20.2 months for the palbociclib arm, which resulted in the accelerated approval of palbociclib in this setting in February 2015. Subsequent phase III data (PALOMA-2) confirmed this doubling of PFS with the use of palbociclib in the frontline setting, and two additional CDK 4/6 inhibitors, ribociclib and abemaciclib, are now on the market. These three agents have extended countless lives when used with aromatase inhibitors as part of first-line therapy for metastatic ER-positive breast cancer. Extraordinarily, the PFS was extended to 40.1 months vs. 21.4 months for letrozole plus placebo. Extension studies (NCT02513394, NCT03155997) or planned (NCT03285412) to look at the use of CDK 4/6 inhibitors in stage II/III high-risk ER-positive breast cancer to see if incorporation of this class of drugs into adjuvant therapy reduces the risk of developing metastatic disease.

mTOR Inhibitors

Inhibitors of mTOR comprise another important chapter in the story of endocrine resistance. mTOR activates ER in a ligand-independent fashion, and hyperactivation of this pathway has been observed in endocrine-resistant breast cancer cells. Therefore, mTOR has become a rational target to enhance the efficacy of hormonal therapy. The BOLERO 2 trial showed that, in patients with ER-positive metastatic breast cancer resistant to letrozole or anastrozole who were given exemestane as the next line of therapy, the mTOR inhibitor everolimus, when given with exemestane, could extend PFS from 4.1 months to 10.6 months. Everolimus is used regularly now in the treatment of patients with metastatic breast cancer, and, like CDK 4/6 inhibitors, is being evaluated in clinical trials in the upfront setting (NCT01674140, NCT01805271). Several other studies (NCT02732119, NCT02871791) looking at triplet combinations—endocrine therapy with CDK 4/6 inhibition and mTOR inhibition—as a way to improve outcomes for patients with stage IV disease.

Investigational Agents

A number of ongoing clinical trials are exploring the optimal combination and sequencing of the above-mentioned therapies in ER-positive metastatic disease and at other possible therapeutic targets. Enzolimatostat is a small molecule of class I histone deacetylases that is thought to prevent the emergence of drug-tolerant clones and to sensitize cells to anticancer therapies. A phase II trial showed that entinostat added to exemestane prolonged PFS compared with exemestane alone (4.3 vs. 2.3 months) and, even more interestingly, extended overall survival even longer (26.9 months vs. 19.8 months). E2112 (NCT02115282) is a phase III randomized controlled trial, the results of which will likely dictate whether entinostat becomes part of the arsenal of therapies available for management of ER-positive metastatic disease.

Mutations in \( ESR1 \), which are found rarely in untreated ER-positive breast cancer, are present in 20% to 50% of those patients who experience progression during treatment with an aromatase inhibitor. These mutations have been shown to predict resistance to additional aromatase inhibitor–based therapy and to suggest better responsiveness to fulvestrant-containing regimens. As a result, a number of companies have developed an interest in designing more potent selective estrogen receptor downregulators that may have potential uses in this population. Bardia et al presented data from a phase I trial of the oral selective estrogen receptor downregulator RAD1901 at the 2017 ASCO Annual Meeting; the study demonstrated a 23% objective response rate among 40 heavily pretreated women with ER-positive, HER2-negative breast cancer.

Ongoing Research in HER2-Positive Breast Cancer

With so many excellent drugs at our disposal to treat HER2-positive disease, the future lies in improved tailoring of therapy. We now have multiple targeted agents for use in the metastatic setting, as described. Others include tucatinib, a potent and selective oral HER2 inhibitor that recently has been granted orphan drug designation for patients with HER2-positive brain metastases and that represents an exciting new option for this group of patients. The HER2CLIMB trial (NCT02614794) is actively enrolling.

Recent studies suggest that HER2-positive disease is highly heterogeneous; the disease incorporates all of the subtypes, especially the HER2-enriched and luminal subtypes. Studies of CDK 4/6 inhibition are ongoing in patients...
with ER+ and HER2+ breast cancers, which typically have lower pCR rates as a result of neoadjuvant HER2-based chemotherapy in the upfront setting; it is believed that crosstalk between HER2 and ER signaling may play a role in tumor resistance and that inhibition of CDK 4/6 may prevent progression of disease in this situation. MonarchHER (NCT02675231) has just closed to accrual, looking at CDK 4/6 inhibition in the third-line setting for metastatic disease, and PATINA (NCT02947685), which started recruiting more recently, brings palbociclib to the first-line metastatic setting.

CONCLUSION

Targeted therapy has been an area of much focus in all malignancies, and this time in our history has been referred to regularly as the era of precision medicine.76 As our understanding of genomics, driver pathways, and mutational evolution deepens, we will continue to move the field forward. Those in the field of breast cancer have already had to ask some of the questions that will shape the future of oncology therapeutics more broadly: Once we understand how to approach a target, how do we change or modify the approach when resistance develops? If we identify targeted treatments that work well in advanced-stage disease, can and should we move them forward into the upfront setting? Can we combine multiple targeted therapies, and at what cost—to the patient and to society? When is doing more too much, and when it is necessary? These are all questions that we will continue to ask ourselves, in the field of breast cancer and beyond, as we refine our definitions of and our approach to precision medicine.

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CANCER PREVENTION, HEREDITARY GENETICS, AND EPIDEMIOLOGY
Lifestyle Modifications and Policy Implications for Primary and Secondary Cancer Prevention: Diet, Exercise, Sun Safety, and Alcohol Reduction
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OVERVIEW

Improved cancer treatments and cancer detection methods are not likely to completely eradicate the burden of cancer. Primary prevention of cancer is a logical strategy to use to control cancer while also seeking novel treatments and earlier detection. Lifestyle modification strategies to improve primary prevention and risk reduction for the development of cancer include choosing a healthy diet with an emphasis on plant sources, maintaining a healthy weight throughout life, being physically active, regularly using sunscreen and wearing protective clothing, limiting sun exposure during the hours of 10 AM to 2 PM, avoiding indoor tanning, and reducing or eliminating alcohol use. In addition to continued use of ongoing education of the public, health care providers, and cancer support communities, other policy and public health efforts should be pursued as well. Examples of supported and successful policy approaches are included in this article, including efforts to limit indoor tanning and improve community-wide interventions to reduce ultraviolet radiation exposure as well as to formally support various alcohol policy strategies including increasing alcohol taxes, reducing alcohol outlet density, improving clinical screening for alcohol use disorders, and limiting youth exposure to alcohol marketing and advertising. These prevention strategies are expected to have the largest impact on the development of melanoma as well as breast, colorectal, head and neck, liver, and esophageal cancers. The impact of these strategies as secondary prevention is less well understood. Areas of additional needed research and implementation are also highlighted. Future areas of needed research are the effects of these modifications after the diagnosis of cancer (as secondary prevention).

The role of diet and physical activity in cancer prevention and survivorship has been widely studied in epidemiology. Expert reports and consensus statements from leading cancer organizations suggest that these modifiable lifestyle behaviors account for between 30% and 50% of cancers.1,2 Several reports, including a systematic review, have demonstrated that if Americans were to adhere to the American Cancer Society (ACS) guidelines for cancer prevention, cancer rates would be reduced by an estimated 17% overall and by up to 60% for select cancers (e.g., colorectal cancer) in high-risk groups.3,4 A major driver of cancer risk is obesity. Over the past several decades, rates of obesity have escalated to epidemic proportions in the United States, increasing cancer risk across the population. It is estimated that obesity accounts for 14% to 20% of the attributable cancer risk for U.S. adults and as much as 50% of all cancers for people younger than age 65.5 A 2016 report from the International Agency for Research on Cancer (IARC)6 listed 13 cancers as “obesity related” and 18-year follow-up data from the Nurses’ Health Study demonstrate adult weight gain as having a major influence on cancer risk in adulthood.7 These findings highlight the need to promote lifelong weight management as an effective strategy to reduce cancer burden.

GUIDELINES FOR CANCER PREVENTION

The ACS8 and the American Institute for Cancer Research/World Cancer Research Fund9 have provided guidelines for cancer prevention (and survivorship) for more than 20 years. These guidelines address several lifestyle behaviors, including avoidance of tobacco products and alcohol, weight management, healthy food choices, and regular physical activity...
as well as timely cancer screening. The guidelines are summarized in Sidebar 1. ACS expanded its recommendations in 2012 to include the following call for community action to improve the diet and exercise of communities:

**PRACTICAL APPLICATIONS**
- Lifestyle behaviors play a substantial role in reducing cancer incidence, comorbidity, and survival.
- As such, clinicians should routinely evaluate lifestyle behaviors and promote healthy lifestyles to reduce the cancer burden.
- Health promotion for cancer risk reduction should include healthy food choices, regular physical activity, reduction or avoidance of alcohol, and sun-protective behaviors.
- Policy strategies are an effective approach to limiting ultraviolet radiation exposure and reducing high-risk alcohol consumption, thereby reducing the incidence of cancer.
- Whether lifestyle behavior changes can influence cancer recurrence or secondary cancer development is an area of needed future research.

Public, private, and community organizations should work collaboratively at national, state, and local levels to implement policy and environmental changes that:

1. Increase access to affordable, healthy foods in communities, worksites, and schools and decrease access to marketing of foods and beverages of low nutritional value, particularly to youth, and
2. Provide safe, enjoyable, and accessible environments for physical activity in schools and worksites and for transportation and recreation in communities.

The American Institute for Cancer Research/World Cancer Research Fund guidelines are continuously reviewed and the epidemiologic evidence evaluating the role of diet, physical activity, and cancer is updated based on new evidence. The ACS guidelines are updated by experts in the field every 5 to 7 years; a 2018 update is currently underway. Among the expected advances will be a greater emphasis on the combined impact of cancer-preventive health behaviors in reducing cancer risk and cancer mortality as well as the need to promote healthy eating patterns, including the Mediterranean diet. In the area of obesity, beyond adult weight gain and high body mass index, guidelines are expected to include...
greater emphasis on metabolic health. Recent evidence suggests that even those with a normal body mass index may demonstrate metabolic dysregulation, which promotes cancer. In addition, work from the Caan laboratory at Kaiser Permanente suggests that beyond adiposity, there is a vital role for lean mass in relation to cancer survival, as evidenced for colorectal cancer.

**MECHANISMS: DIET AND PHYSICAL ACTIVITY MODULATION OF CANCER RISK**

In addition to the substantial epidemiologic evidence demonstrating relationships between diet, physical activity, and cancer, there are relevant biologic mechanisms that support a modifying effect of these lifestyle exposures on cancer risk and recurrence, as illustrated in Figure 1.

Diet, physical activity, and weight control each have independent and potentially additive effects on these cancer-modulating biologic mechanisms. Healthy lifestyle choices promote a cancer-suppressing environment at the host/systemic, organ/tissue, and DNA/genetic levels, thus amplifying the potential together to reduce cancer risk.

**EVIDENCE FROM RANDOMIZED CONTROLLED TRIALS**

The evidence supporting a role for diet and physical activity in cancer risk reduction is largely limited to epidemiology. A few randomized controlled trials have been conducted. The largest trial was the Women’s Health Initiative, which included an evaluation of a low-fat diet for the prevention of breast and colorectal cancer as well as the role of vitamin D plus calcium supplementation. These trials showed no significant (p = .07 for ref 14, p = .51 for ref 15) overall reduction in cancer risk after an estimated 8 years of follow-up. There was a 9% lower risk for breast cancer among women randomly assigned to the low-fat diet who entered the trial with higher dietary fat intake. The SELECT trial showed no reduction in prostate cancer risk with selenium and vitamin E supplementation, similar to null or even adverse findings from other supplement trials with compounds such as beta-carotene (CARET study) or B vitamins (VITAL study). There are currently essentially no randomized controlled trials evaluating the effect of physical activity on cancer risk.

In the area of cancer survivorship, randomized controlled trials have largely focused on modulation of intermediate biomarkers of cancer risk, including many of the mechanistic biomarkers defined in Figure 1. In general, the trials conducted have been focused on the more common cancers—predominantly breast cancer, as well as prostate, colorectal, and endometrial cancers. The impact of interventions on cancer-related outcomes is summarized with select studies in Table 1.

In summary, the role of diet, physical activity, and weight management in cancer prevention and survivorship is well established in terms of the epidemiologic evidence and biologic plausibility. Randomized controlled trials remain sparse and are largely focused on recurrent disease among cancer survivors. The effect of interventions has been demonstrated but not consistently, particularly when recruitment includes relatively “healthy” volunteers. Recommendations for obesity clinical trials in cancer survivorship have been published, including a 2015 report from ASCO. Guidelines suggest that trials be conducted by multidisciplinary teams, focus on more common obesity-related cancers with higher mortality or recurrence risk, and be statistically powered to evaluate cancer outcomes and economic endpoints as well as current approaches focused largely on intermediate biomarkers. Priority should be given to translating the evidence for diet, activity, and weight management into clinical and community practice as recommended by the National Comprehensive Cancer Network and others.
TABLE 1. Select Lifestyle Intervention Trials and Related Health Outcomes in Cancer Survivorship

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Reference</th>
<th>Population</th>
<th>Number of Participants</th>
<th>Diet</th>
<th>Physical Activity</th>
<th>Weight Loss</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHEL</td>
<td>Pierce et al (2007)(^2)</td>
<td>Breast cancer survivors</td>
<td>3,088</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to either a telephone-based intervention of five servings of vegetables per day, 16 ounces of vegetable juice per day, three servings of fruit per day, and 30 g of fiber per day vs. usual care (five a day)</td>
<td>No difference in breast cancer recurrence between groups; however, secondary analyses revealed that women in the highest quartile of plasma carotenoids experienced a reduced risk of recurrence</td>
</tr>
<tr>
<td>WINS</td>
<td>Chelbowski et al (2006)(^3)</td>
<td>Breast cancer survivors</td>
<td>2,437</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to either a low-fat (&lt; 15% calories from fat) in-person intervention or usual care</td>
<td>No difference between groups for overall disease progression; however, survival differences observed by hormone status for women most adherent to the diet</td>
</tr>
<tr>
<td>PAL</td>
<td>Schmitz et al (2010)(^4)</td>
<td>Breast cancer survivors with lymphedema or at risk for lymphedema</td>
<td>154</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to either a 13-week supervised weight-lifting intervention followed by unsupervised exercise for 9 months vs. no exercise control</td>
<td>Exercise intervention did not increase risk for lymphedema among women at high risk for developing lymphedema and decreased symptoms of lymphedema among women with lymphedema</td>
</tr>
<tr>
<td>RENEW</td>
<td>Morey et al (2009)(^5)</td>
<td>Overweight, older breast and prostate cancer survivors</td>
<td>641</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>RCT with assignment to a waitlist control or a 12-month home-based tailored print and telephone-based intervention aimed at increasing healthy lifestyle behaviors and modest weight loss</td>
<td>Significant increases in physical activity, diet quality, and quality of life and a 2-kg weight loss difference in intervention vs. control participants</td>
</tr>
<tr>
<td>Yale Exercise Study</td>
<td>Jones et al (2013)(^6)</td>
<td>Breast cancer survivors</td>
<td>75</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to a 6-month aerobic exercise intervention vs. usual care</td>
<td>No observed differences between groups on markers of inflammation. Secondary analysis among women meeting 80% of the exercise goal demonstrated reductions in interleukin-6</td>
</tr>
<tr>
<td>LIVESTRONG YMCA</td>
<td>Irwin et al (2017)(^7)</td>
<td>All cancer types, 53% breast cancer</td>
<td>186</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to the YMCA LIVESTRONG exercise program vs. control</td>
<td>71% vs. 26% met &gt; 150 minutes of physical activity per week, and improved distance in the 6-minute walk test and overall quality of life in the intervention vs. control arm</td>
</tr>
<tr>
<td>LEAN</td>
<td>Harrigan et al (2016)(^8)</td>
<td>Overweight breast cancer survivors</td>
<td>100</td>
<td>X</td>
<td></td>
<td></td>
<td>RCT with assignment to usual care vs. in-person or telephone-based weight loss intervention</td>
<td>Women assigned to the in-person intervention lost 6.4% of body weight vs. 5.4% and 2.0% in the telephone and usual care groups, respectively. Those in the intervention arms also had a 30% reduction in hsCRP</td>
</tr>
</tbody>
</table>

Continued
## TABLE 1. Select Lifestyle Intervention Trials and Related Health Outcomes in Cancer Survivorship (Cont’d)

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Reference</th>
<th>Population</th>
<th>Number of Participants</th>
<th>Diet</th>
<th>Physical Activity</th>
<th>Weight Loss</th>
<th>Intervention</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRESH START</td>
<td>Demark-Wahnefried et al (2007)(^{26})</td>
<td>Breast and prostate cancer survivors</td>
<td>543</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>RCT with assignment to nontailored print vs. tailored print materials for improving healthy lifestyle behaviors</td>
<td>Both groups improved; however, the tailored print group experienced greater gains in minutes of exercise per week (+59 vs. +39 minutes), fruit and vegetable intake (+1.1 vs. +0.6 servings per day), and BMI (−0.3 vs. +0.1 kg/m(^2))</td>
</tr>
<tr>
<td>CanChange</td>
<td>Hawkes et al (2013)(^{27})</td>
<td>Colorectal cancer survivors</td>
<td>410</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>RCT with assignment to either usual care or a telephone-based health coaching intervention for 6 months</td>
<td>Participants in the intervention increased moderate to vigorous physical activity by 28.5 minutes per week and 0.4 servings of fruits and vegetables per day compared with the control and decreased calories from fat by 7% and BMI by 0.9 kg/m(^2)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; hsCRP, high-sensitivity C-reactive protein; RCT, randomized controlled trial.
MELANOMA PREVENTION: LIFESTYLE CHANGES AND LEGISLATION

In 2018, it is estimated that 91,270 individuals will be diagnosed with melanoma, the most lethal form of skin cancer.31 Although the rate of almost all cancers is decreasing, the incidence of melanoma continues to rise34; melanoma is clearly a major public health problem.35 Tempering some of the concerns related to these observed trends, early-stage melanoma (the most common melanoma diagnosis in the United States) is generally associated with a favorable outcome. For patients with advanced disease, whose survival has historically been measured in months, unprecedented antitumor activity and evolving survival benefit from novel targeted therapies and immunotherapies have ushered in a new era for patients with unresectable and/or metastatic melanoma; these therapeutic advances are also beginning to favorably impact survival for patients in the adjuvant arena.36-45

Fortunately, advances in our understanding of risk factors associated with melanoma have also matured. There is compelling evidence that ultraviolet radiation (UVR) exposure contributes to melanoma risk.46,47 In 2009, UVR from the sun or from indoor tanning devices was classified as a class I carcinogen by the World Health Organization IARC.47 Indeed, nearly 95% of all skin melanoma cases and deaths in the United States are attributable to UVR.48 Recommendations for reducing melanoma risk focus on minimizing overexposure to the sun and avoiding use of indoor tanning. In the absence of new public health interventions, it is estimated that by 2030, 112,000 new invasive melanomas (i.e., exclusive of melanoma in situ) will be diagnosed in the United States.43,49

Lifestyle recommendations for melanoma prevention include regularly using sunscreen and wearing protective clothing, seeking shade and limiting time outdoors during the hours of 10 to 2, and avoiding indoor tanning.43,50 Recent studies from Norway51 and Australia52 have shown that regular sunscreen use by adults reduces melanoma risk. Sun-protection practices are also important for youth; having five or more blistering sunburns while young has been estimated to increase the risk of melanoma by 80%.48 Increasing ongoing sun exposure in childhood and throughout one’s lifetime is known to be associated with an increased risk of skin cancer and melanoma.53 The risk of melanoma is also higher among those who initiate indoor tanning at a young age and those who frequently indoor tan.54,55

Unfortunately, preventive practices are not regularly followed. Based on the 2013 Youth Risk Behavior Survey, a nationally representative sample of high school students, only 10% reported using sunscreen with a sun protection factor of 15 or higher always or most of the time when outside for more than 1 hour on a sunny day.56 In addition, most respondents (56%) reported having one or more sunburns in the prior year.56 Access to tanning facilities also helps support the practice of indoor tanning; the number of tanning facilities exceeds that of Starbucks and McDonald’s restaurants in more than 100 major U.S. cities.57

Recognizing the importance of establishing skin cancer prevention as a national priority, The Surgeon General’s Call to Action to Prevent Skin Cancer was released in July 2014. This call to action described prevention strategies and called on all community sectors to play a role in protecting Americans from UVR from the sun and artificial sources.50 It set forth five main goals50 that if successfully and broadly enacted could significantly reduce the burden of skin cancer in the United States (Sidebar 2). Strategies that support goals related to lifestyle modifications to reduce the burden of melanoma are outlined below.

Reducing the Harms From Indoor Tanning

There is compelling evidence that artificial UVR exposure from indoor tanning is an independent risk factor for melanoma.54,55,58,59 Moreover, data from The Cancer Genome Atlas initiative reveal that cutaneous melanoma has the highest somatic mutation rate of all tumors explored, and underlying mutations demonstrate transition patterns associated with a ultraviolet signature.60,61 Despite convergence of epidemiologic and genetic data, an estimated 11.3 million people in the United States engaged in indoor tanning in 2013, 1.6 million of whom were younger than age 18.62,63 Based on a recent Centers for Disease Control and Prevention analysis, if no minors currently age 14 and younger ever indoor tanned as minors (younger than age 18), more than 61,000 cases and more than 6,700 deaths would be averted.64 If the same cohort of youth never indoor tanned during their lifetimes, more than 200,000 melanoma cases and more than 23,000 melanoma deaths would be averted, saving nearly $1.1 billion in lifetime treatment costs.64

Several legislative and regulatory practices have been implemented to address the harms of indoor tanning. In 2014, the U.S. Food and Drug Administration (FDA) reclassified tanning devices from “low-risk” class I to “moderate-risk” class II, added a visible “black box” warning, and required stricter controls for design and safety.65 In December 2015, the FDA proposed a federal rule restricting minors’ access to tanning beds and requiring that sunlamp manufacturers and tanning

SIDEBAR 2. The U.S. Surgeon General’s Call to Action to Prevent Skin Cancer: Five Strategic Goals

- Increase opportunities for sun protection in outdoor settings
- Provide individuals with information to make informed, healthy choices about ultraviolet radiation exposure
- Promote policies that advance the national goal of preventing skin cancer
- Reduce the harms from indoor tanning; and
- Strengthen research, surveillance, monitoring, and evaluation related to skin cancer prevention.

Adapted from the U.S. Department of Health and Human Services.50
facilities take additional measures to improve the overall safety of these devices; this is currently on hold. In 2012, the first two states enacted legislation to restrict minors younger than age 18 from indoor tanning facilities. As of January 2018, 17 states and the District of Columbia have prohibited indoor tanning among minors younger than age 18 (Fig. 2). Importantly, there are evolving data to support that these legislative and regulatory initiatives are having an impact. In a study in Texas, 81% of tanning facilities contacted in a mystery shopping–style study were compliant. Furthermore, results from the 2015 Youth Risk Behavior Survey and the National Health Interview Survey showed a significant decline in indoor tanning among both students and adults (Figs. 2 and 3).

Efforts continue to empower policymakers to make informed decisions regarding the dangers of indoor tanning, such as those led by the ACS–Cancer Action Network, a nonprofit advocacy affiliate of the ACS. As part of its coordinated commitment to melanoma prevention, a collaborative and multidisciplinary research initiative known as the Moon Shots Program, The University of Texas MD Anderson Cancer Center (MD Anderson) served as the primary scientific and clinical resource for the Texas Legislature in 2013 on adoption of a law prohibiting tanning beds for minors younger than age 18. MD Anderson partners with the ACS–Cancer Action Network to share lessons learned and disseminate the policy to other states. Aligning these approaches with education about the harms of indoor tanning and UVR overexposure, beginning with our youth, holds tremendous promise toward reducing the burden of melanoma.

Youth Education Approaches

In the United States, approximately 55 million students will attend public and private elementary and secondary schools. Because UVR overexposure increases the risk of melanoma, it is important to implement skin cancer prevention initiatives early, making schools an ideal setting for such efforts. Recognizing the need to reach children early,
MD Anderson developed Ray and the Sunbeatable, a sun safety program for preschoolers, kindergarteners, and first-grade students as part of the melanoma prevention initiative of the Moon Shots Program. This evidence-based curriculum educates children, parents, and teachers about sun protection and promotes sun safety behaviors. In the later grades, programs such as SunWise and SunSmart have been instrumental in increasing sun safe messages throughout the United States and Australia to effect lifestyle change. According to the 2014 School Health Policies and Practices Study, 66% of U.S. elementary, middle, and high schools implemented sun safety or skin cancer prevention instruction. Despite this progress, fewer than one-half of schools recommend and almost no schools require policies and practices related to sun safety, such as allowing or encouraging students to apply sunscreen while at school, encouraging students to wear sun-protective clothing, or scheduling outdoor activities when the sun is not at peak intensity. Moreover, many states have rules or policies that may make using sunscreen or being protected from the sun more difficult, such as restrictions on wearing hats during the school day. Furthermore, the FDA considers sunscreen as an over-the-counter drug product; as a result, in some schools, students are prohibited from bringing sunscreen without a note from a physician. To address the issue of limited sunscreen availability, an increasing number of states have adopted legislation to allow children to possess and use sunscreen on public school property and at school events.

Community-Wide Interventions Focused on Modifying Healthy Behaviors Including Decreasing UVR Exposure

The Community Preventive Services Task Force, an independent, nonfederal panel of public health and prevention experts that provides evidence-based recommendations about community preventive interventions, conducted a comprehensive systematic review of interventions for skin cancer. They identified five areas for implementation: (1) child care center–based interventions, (2) primary and middle school–based interventions, (3) interventions in outdoor occupational settings, (4) interventions in outdoor recreational and tourism settings, and (5) multicomponent community-wide interventions.

Multicomponent community-wide interventions to prevent skin cancer combine individual-directed strategies (e.g., items 1-4 above), mass media campaigns, and environmental and policy changes across multiple settings within a defined geographic region in an integrated effort to influence ultraviolet-protective behaviors. These interventions have been shown to prevent skin cancer by increasing ultraviolet-protective behaviors by increasing sunscreen use. An example of this type of programming is being implemented by MD Anderson’s Be Well Communities, a community-driven, place-based approach to cancer prevention and control.

Another important feature of the community-wide approach is that it can simultaneously target multiple aspects of cancer prevention; successful implementation can have a beneficial multiplicative effect by favorably impacting lifestyles that support cancer prevention initiatives. For example, one way to address obesity, which is itself a risk factor for cancer (as described above), is to increase physical activity. If individuals are encouraged to be physically active outdoors in a way that also addresses prolonged periods of sun exposure, multiple beneficial endpoints may be achieved. For example, increased active use of parks has been linked to the availability of shade and/or shade-providing devices among parents and/or caregivers.

In summary, abundant epidemiologic and genetic data support the role of UVR exposure in increasing melanoma risk. Development and successful implementation of primary prevention strategies that support The Surgeon General’s Call to Action have the capacity to reduce melanoma risk. Lifestyle changes—informed and promulgated by broad- and evidence-based educational programs, legislative efforts, and multicomponent community-wide initiatives—represent important elements of an overall...
effort to significantly reduce the public health burden of melanoma in the future.

ADDRESSING ALCOHOL AS AN APPROACH TO CONTROL CANCER

ASCO has recently joined a number of other international cancer care and public health organizations in supporting measures to reduce high-risk alcohol consumption. In its recently published statement on alcohol and cancer,87 which represents its first formal statement on the topic, the ASCO Cancer Prevention Committee outlines a number of specific goals. Namely, in publishing the aforementioned statement, the committee seeks to educate the public regarding the causal link between alcohol abuse and cancer, support policy changes to curtail excessive alcohol use, educate oncology providers regarding the role of alcohol in carcinogenesis, and identify research needs to further explore the role of alcohol in cancer risk.

Epidemiology of Alcohol-Related Cancers

The cancer burden attributable to alcohol is significant. In 2012, an estimated 6.6% of worldwide cancer deaths were attributable to alcohol.89 In the United States, alcohol accounted for roughly 3.5% of cancer deaths for 2009. Upper airway and esophageal cancers accounted for the majority of alcohol-attributable deaths among men. Breast cancer accounted for the majority among women.89 Additional cancers causally linked to alcohol include hepatocellular carcinoma and colorectal cancer.90 Cancer risk correlates with increasing alcohol consumption for cancers in which alcohol is implicated.5,93

In its 2010 monograph on the evaluation of carcinogenic risk to humans, the IARC outlines alcohol as a cause of the aforementioned cancer types (oral cavity, pharynx, larynx, squamous cell carcinoma of the esophagus, colorectum, liver, and female breast) after thorough assessment of the evidence.93 In this same report, the question of type of alcoholic beverage is addressed. The conclusion is that the cancer risk appears to be linked to ethanol irrespective of the specific alcoholic beverage (e.g., beer, wine, or hard liquor).93

Alcohol has been implicated in a number of other cancers as well, and the full breadth of causal relationships remains to be determined definitively. For example, suspicion that alcohol causes gastric and lung cancers is high based on several studies. However, strong correlations with other risk factors (i.e., *Helicobacter pylori* infection in gastric cancer and smoking in lung cancer) has led to an inability to establish alcohol as an independent risk factor.93

Carcinogenic Mechanisms of Alcohol

It is clear that alcohol plays an important role in carcinogenesis, and evidence points to the fact that the specific alcoholic beverage does not meaningfully propagate or mitigate risk.5 Recall that ethanol is eliminated from the body by oxidation to acetaldehyde—mediated by alcohol dehydrogenase—and eventually to acetate. Although the exact mechanism by which alcohol leads to carcinogenesis remains unclear, animal models suggest that it is acetaldehyde rather than ethanol itself that is carcinogenic and mutagenic.94

The IARC undertook a review of the role of alcohol in carcinogenesis. In its 2012 monograph on the evaluation of carcinogenic risks in humans,94 the IARC synthesized evidence from a number of sources supporting alcohol as a carcinogen. Mice and rat data on the oral consumption of ethanol/acetaldehyde show an increase in the incidence of a number of tumor types compared with controls.94 Coadministration of alcohol with known carcinogens in the drinking water of rats and mice further enhanced tumor growth.94

The IARC monograph goes on to discuss the oxidative pathway by which alcohol is metabolized and concludes that those persons with impaired ability to oxidize acetaldehyde (e.g., those with one inactive allele coding for the aldehyde dehydrogenase-2 [ALDH2] enzyme) to acetate are at increased risk to develop alcohol-related cancers.94 East Asian populations have the highest prevalence of a high-risk genetic variant [(rs671)*2] of *ALDH2*. This variant encodes an inactive form of the ALDH2 enzyme. Studies involving these East Asian populations correlate the presence of the high-risk genotype with increased risk of cancers of the upper aerodigestive tract.95

The IARC authors outline a number of additional carcinogenic mechanisms. These mechanisms include oxidative stress, increased androgen/estrogen production, enhanced liver fibrogenesis, and decreased folate concentrations.96 Moreover, the role of direct contact of acetaldehyde with cell surfaces should be noted, particularly given the distribution of cancers clearly associated with alcohol consumption. Acetaldehyde formation begins in the oral cavity, primarily mediated by oral bacteria. The highest levels of acetaldehyde are indeed within the saliva of the oral cavity immediately after alcohol consumption, corresponding with the sites of cancers most strongly linked to alcohol consumption.95

Dose-Response Relationship

Understanding the dose-response relationship between cancer risk and alcohol consumption is important for a number of reasons. Understanding the cancer risk increase relative to increase in alcohol consumption is important for educating patients. Moreover, appreciating when cancer risk begins to increase as it relates to alcohol consumption furthers our understanding as oncology practitioners, better allowing us to counsel patients.

Table 2 summarizes the results of a large meta-analysis addressing the relative risks of cancers linked to alcohol relative to the amount of alcohol being consumed. Light drinking, moderate drinking, and heavy drinking correspond to consuming 12.5 g or less, 50 g or less, and more than 50 g of alcohol per day, respectively. As a point of reference, a standard drink was considered to contain 12.5 g of alcohol.92

Table 2 demonstrates multiple valuable points. First, note that the magnitude of risk differs for different cancer types, with the greatest risk noted for cancers of the oral cavity and pharynx. For heavy drinkers, the relative risk of oral cavity and pharyngeal cancers was more than five times that of nondrinkers. Not surprisingly, the greatest risks were seen in cancers where alcohol and its metabolites come in direct
that “If alcoholic drinks are consumed, limit consumption to with the World Cancer Research Fund recommended in conjunction were evident. In the setting of the above findings, the American Institute for Cancer Research in conjunction with the World Cancer Research Fund recommended that “If alcoholic drinks are consumed, limit consumption to two drinks a day for men and one drink a day for women.” Furthermore, they also recommended that “For cancer prevention, it’s best not to drink alcohol.”

Public Health Strategies to Control Alcohol Use

With the relationship between alcohol and increased cancer risk well evidenced, the ASCO Cancer Prevention Committee statement moves to promote meaningful change through public health strategies. In so doing, ASCO joins a chorus of international cancer care and public health organizations already calling for such changes. Such policies are also evidence based. ASCO specifically outlines strategies including, but not limited to, the following:

1. Develop clinical strategies to screen for at-risk alcohol use and provide treatments and/or referrals for those in need of services.
2. Reduce alcohol outlet density. Reduction of sites of legal alcohol sale has proven to be an effective strategy in previous experiences.
3. Increase taxation and pricing of alcoholic beverages. These increases have been shown previously to reduce excessive consumption.
4. Restrict youth exposure to advertising of alcohol. Drinking at a young age leads to increased risk of alcohol dependence.

Areas of Needed Research and the Role of the Oncologist

Looking to the future, research questions in need of investigation are numerous. Although the causal link between alcohol and some cancers is clear, increased knowledge regarding the mechanisms underpinning cancer risk is needed. The effects of concurrent use of alcohol while undergoing treatment with surgery, radiation, chemotherapy, or any combination of therapies are largely unknown. The broader question of how to best intervene in the general community to reach those at risk for alcohol-related cancers remains unanswered; in a similar vein, the cancer survivorship community is in need of evidence-based interventions to address high-risk alcohol use in an effort to curb secondary cancers related to alcohol.

The oncologist stands at the forefront of addressing the issue of alcohol-related cancer risk. The oncologist plays a critical role in treating cancers arising from alcohol use but perhaps more importantly, he or she is a critical voice in the prevention of such cancers—both prior to an initial cancer diagnosis and in the capacity of preventing subsequent malignancies. The aforementioned research questions are left to the oncologist to answer. Taken as a whole, the oncology community and the practitioners within it are charged with addressing a culture, both in the United States and worldwide, that is very accepting and often promoting of alcohol use. Perhaps the single greatest task before us is to promote an honest recognition of the risks of alcohol, even in moderation.

CONCLUSION

Although cancer incidence and death rates are decreasing, the burden of cancer remains high in the United States and globally. Preventing cancer from developing, where possible, is a key method for reducing the burden of cancer. Primary prevention of cancers is possible via potentially modifiable lifestyle changes, including maintaining a healthy weight, obtaining regular physical activity, avoiding high-risk sun exposures, and limiting alcohol intake. Guidelines have been published by various agencies with

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**TABLE 2. Summary of the Relative Risks From a Meta-Analysis for the Association Between Amount of Alcohol Drinking and Risk of Cancer**

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Nondrinker</th>
<th>Light Drinker (&lt; 1 Drink per Day)</th>
<th>Moderate Drinker (2–4 Drinks per Day)</th>
<th>Heavy Drinker (&gt; 4 Drinks per Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity and pharynx</td>
<td>1.0 (referent)</td>
<td>1.13 (1.0–1.26)</td>
<td>1.83 (1.62–2.07)</td>
<td>5.13 (4.31–6.10)</td>
</tr>
<tr>
<td>Esophageal squamous cell</td>
<td>1.0 (referent)</td>
<td>1.26 (1.06–1.50)</td>
<td>2.23 (1.87–2.65)</td>
<td>4.95 (3.86–6.34)</td>
</tr>
<tr>
<td>Larynx</td>
<td>1.0 (referent)</td>
<td>0.87 (0.68–1.11)</td>
<td>1.44 (1.25–1.66)</td>
<td>2.65 (2.19–3.19)</td>
</tr>
<tr>
<td>Liver</td>
<td>1.0 (referent)</td>
<td>1.00 (0.85–1.18)</td>
<td>1.08 (0.97–1.20)</td>
<td>2.07 (1.66–2.58)</td>
</tr>
<tr>
<td>Female breast</td>
<td>1.0 (referent)</td>
<td>1.04 (1.01–1.07)</td>
<td>1.23 (1.19–1.28)</td>
<td>1.61 (1.33–1.94)</td>
</tr>
<tr>
<td>Colorectal</td>
<td>1.0 (referent)</td>
<td>0.99 (0.95–1.04)</td>
<td>1.17 (1.11–1.24)</td>
<td>1.44 (1.25–1.65)</td>
</tr>
</tbody>
</table>

Adapted with permission from LoConte et al.87
recommendations for recommended lifestyle modifications. This specifically has implications for breast, colorectal, head and neck, esophageal, and liver cancers and melanoma. The role of lifestyle modifications for secondary prevention is less well understood, and this is a critical area for future research.

References


100. Livingston M, Chikritzhs T, Room R. Changing the density of alcohol outlets to reduce alcohol-related problems. Drug Alcohol Rev. 2007;26:557-566.


Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention

Matthew B. Yurgelun, MD, and Heather Hampel, MS, LGC

## OVERVIEW

Identification of individuals with inherited predispositions to cancer, including Lynch syndrome, can help prevent cancer and cancer-related death by allowing for the uptake of specific cancer prevention and screening as well as the use of therapies directed toward the underlying neoplastic process for individuals with advanced cancer. In the 25 years since the discovery of microsatellite instability (MSI) and the first recognition of germline mismatch repair (MMR) gene variants as the etiologic basis of Lynch syndrome, there has been tremendous progress in the understanding of the spectrum of cancer risk associated with Lynch syndrome as well as in cancer prevention and risk-reduction strategies. The past few years, in particular, have brought transformative changes in the treatment of Lynch syndrome–associated cancers with immune checkpoint inhibitors. In parallel, advances in next-generation sequencing (NGS) technologies now allow rapid and scalable somatic and germline sequencing that promises to help identify Lynch syndrome in individuals who otherwise lack classic phenotypes. Last, real progress is being made to understand more sophisticated methods of precision cancer prevention, including chemotherapeutic prevention agents (e.g., aspirin) and strategies that leverage the immune system to facilitate primary cancer prevention in otherwise-healthy Lynch syndrome carriers.

University of Michigan pathologist Aldred Warthin, MD, PhD, is widely credited as the first person to describe the cancer predisposition syndrome now known as Lynch syndrome (formerly called hereditary nonpolyposis colorectal cancer [HNPCC]) when, in 1895, his seamstress correctly predicted that she would die as a result of cancer after she watched numerous family members succumb to cancers of the gastrointestinal or gynecologic tract. During Warthin’s time and past the mid-20th century, the prevailing notion was that inherited cancer risk did not exist outside of rare conditions, such as familial adenomatous polyposis, in which there was an obvious premalignant phenotype. Now, more than 120 years later, Lynch syndrome is known as one of the most common forms of inherited cancer predisposition; the general population prevalence (estimated at 1 in 279) rivals that of germline BRCA1/BRCA2 variants. Although most classically associated with increased risks of colorectal and endometrial cancers, Lynch syndrome predisposes individuals to a wide array of malignancies, including ovarian, gastric, urinary tract (kidney, renal pelvis, ureter, bladder, and prostate), pancreaticobiliary, small intestinal, and brain cancers, as well as sebaceous neoplasms of the skin and possibly slightly increased risks of female breast cancer and prostate cancer (Table 1). Lynch syndrome is caused by pathogenic germline variants in the DNA MMR genes MLH1, MSH2, MSH6, or PMS2 (and, rarely, in the non-MMР gene EPCAM, in which deletions induce epigenetic silencing of MSH2).

When the MMR genes were identified as the underlying genetic etiology of Lynch syndrome in the early 1990s, little was known about the optimal means of diagnosis of families with Lynch syndrome or prevention of Lynch-associated cancers, and the malignancies that developed were treated in exactly the same way as their sporadic counterparts. With groundbreaking advances in germline and somatic sequencing, clinical risk prediction models, immuno-oncology, and precision cancer prevention, our ability to identify, prevent, and durably treat cancers associated with Lynch syndrome continues to grow in both scope and sophistication.

### DIAGNOSING LYNCH SYNDROME

Currently, there are two general approaches to the diagnosis of Lynch syndrome: (1) molecular screening of colorectal and endometrial tumor specimens for evidence of defective MMR function (MMR-D) or high-level MSI (MSI-H) to identify patients with cancer who should undergo germline testing for pathogenic MMR gene variants; or (2) direct germline testing performed on patients whose personal and/or family histories of cancer are suspicious for Lynch syndrome. Molecular testing has garnered particular attention...
in recent years because of its sensitivity and specificity for identification of Lynch syndrome probands, as well as because of the ever-growing prognostic and therapeutic implications. From the standpoint of Lynch syndrome diagnosis, four main pathology tests can aid in the molecular identification of patients with cancer who are likely to have Lynch syndrome: (1) polymerase chain reaction (PCR)–based MSI testing; (2) immunohistochemical staining (or immunohistochemistry [IHC]) for the MMR proteins; (3) MLH1 promoter methylation analysis (or somatic BRAF V600E mutation analysis); and (4) next-generation somatic (and/or germline) sequencing assays.

**Microsatellite Instability Testing**

MSI in colorectal cancers was first described in 1993 and was quickly recognized as a hallmark characteristic of Lynch syndrome–associated cancers. MSI is defined as changes in the length of repetitive DNA sequences (typically mono- or dinucleotide repeat sequences) in tumors compared with the length of the same microsatellite loci in normal non-neoplastic tissue. This slippage develops as a result of defective DNA MMR machinery, which is characteristic in Lynch syndrome. Historically, five microsatellite loci are evaluated by PCR; if more than 20% are unstable, the tumor is considered to have MSI-H. More recently, it has been shown that MSI status can be directly assessed by NGS of tumors either by direct assessment of numerous microsatellite loci or by assessment of a tumor’s overall mutational burden as a surrogate for MSI status.

**MLH1 Methylation and BRAF Mutation Analyses**

Most MMR-D and MSI-H colorectal and endometrial cancers do not develop because of Lynch syndrome but instead because of an acquired somatic MMR gene inactivation. In the most common such situation, MLH1 function is silenced by acquired methylation of the MLH1 promoter region. This is more common in women and in elderly patients and accounts for 69% of all colorectal cancer occurrences that have an absence of MLH1 and PMS2 on IHC. Most MLH1 promoter methylation accounts for 94% of endometrial cancer occurrences that have an absence of MLH1 and PMS2. Because MLH1 promoter methylation is so common, it is typical to rule it out before germline genetic testing in patients with MSI-H tumors and/or those tumors that demonstrate an absent expression of the MLH1 and PMS2 proteins on IHC. This elimination can be done by directly assessing methylation of the MLH1 promoter region, which is the most sensitive and specific approach at ruling out Lynch syndrome in such cases, but it requires DNA extraction and bisulfite treatment of the DNA that is not readily available at most hospitals. In colorectal cancers, promoter methylation also can be assessed indirectly by testing for the presence of somatic BRAF V600E mutations, as a surrogate for MLH1 methylation status. Somatic BRAF V600E mutations occur in a small fraction of colorectal cancers overall but are found in 69% to 78% of colorectal cancers with MLH1 promoter methylation and are virtually never seen in Lynch syndrome–associated cancers, so BRAF mutation has a high negative predictive value. Some centers have adopted a hybrid model of testing in which BRAF V600E mutation analysis is performed first and, if negative, is followed by MLH1 methylation testing; other centers have switched entirely to MLH1 methylation testing, because it is applicable for both colorectal and endometrial cancers. BRAF V600E mutation analysis is not useful to determine whether MMR-D/MSI-H endometrial cancers are Lynch associated.) Regardless of the strategy, use of MLH1 promoter methylation and/or BRAF mutation analyses can reduce the number of patients who need germline MMR gene testing by half.

**Other Forms of Biallelic Somatic MMR Gene Inactivation**

Recently, it has become more widely understood that other mechanisms can induce somatic biallelic inactivation of
MMR gene function and result in MSI-H cancers with other patterns of MMR-D by IHC. Among unselected colorectal cancer occurrences, this phenomenon appears to be almost as common as Lynch syndrome itself, although it has become widely recognized only in recent years. Individuals with confirmed biallelic somatic MMR gene alterations do not have Lynch syndrome and should be treated according to their clinical history rather than according to Lynch syndrome surveillance guidelines. Testing for these other forms of biallelic somatic MMR gene inactivation typically occurs after abnormal tumor screening and unrevealing germline genetic testing for pathogenic MMR variants, which results in a tumor with unexplained MMR-D. As such testing becomes quickly and increasingly inexpensive, however, it may become advantageous to simply order paired tumor and germline sequencing as a single test, both to streamline workflows and to minimize confusion about non-Lynch MMR-D/MSI-H findings.

Universal Tumor Screening for Lynch Syndrome

In the past, MMR IHC was more cost effective than MSI testing for programs that universally screened all colorectal tumors for Lynch syndrome, particularly because it predicted the MMR gene in which a pathogenic germline variant was most likely. However, with the advent of NGS-based germline testing, there is negligible incremental cost to test all MMR genes, or even to perform germline testing with a broader panel of cancer susceptibility genes beyond the five linked to Lynch syndrome. Furthermore, it has become standard practice to assess all metastatic colorectal cancers for somatic alterations in KRAS, NRAS, and BRAF to guide therapeutic decision-making. Addition of somatic analysis of the standard microsatellite loci and/or even the MMR genes themselves into such testing is a logical next step that likely will streamline universal tumor testing programs, at least for metastatic colorectal cancers.

### TABLE 1. Spectrum of Cancers Associated With Lynch Syndrome and Proven Prevention Strategies

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Estimated Cumulative Cancer Risk (%)</th>
<th>Prevention Strategies</th>
</tr>
</thead>
</table>
| Colorectal cancer | 10–82* | • Frequent (every 1–2 years) colonoscopy reduces incidence and mortality; typically begin at age 20–25  
• Aspirin (600 mg/day) for ≥ 2 years reduces incidence**  
• Subtotal colectomy recommended vs. segmental resection in the setting of known Lynch-associated colorectal cancer |
| Endometrial cancer | 15–60 | • Risk-reducing hysterectomy reduces incidence, but no proven mortality benefit  
• Observational data suggest protective benefit of exogenous progestins  
• No proven benefit to endometrial cancer screening, although guidelines recommend consideration of transvaginal ultrasound and endometrial biopsy beginning at age 30–35 until hysterectomy |
| Ovarian cancer | 1–38 | • Risk-reducing salpingo-oophorectomy reduces incidence, but no proven mortality benefit  
• No proven benefit to ovarian cancer screening, although guidelines recommend consideration of upper endoscopy to biopsy for Helicobacter pylori |
| Gastric cancer | < 1–13 | • No proven benefit to screening, but guidelines recommend consideration of upper endoscopy to biopsy for Helicobacter pylori |
| Urinary tract cancer (kidney, renal pelvis, ureter, and bladder) | < 1–18† | • No proven benefit to screening; one study of urine cytology screening demonstrated 29% sensitivity and high rate of false-positive screens² |
| Small bowel cancer | < 1–6 | • No data to suggest benefit to screening |
| Pancreatic cancer | 1–6 | • No data to suggest benefit to screening, although some guidelines recommend consideration of screening MRI and/or endoscopic ultrasound in the setting of a family history of pancreatic cancer² |
| Biliary tract cancer | < 1–4 | • No data to suggest benefit to screening |
| Female breast cancer | 11–56‡ | • No data to suggest benefit to increased screening compared with the general population |
| Prostate cancer | 17–38‡ | • No data to suggest benefit to increased screening compared with the general population |
| Sebaceous adenomas/carcinomas (skin) | 1–9 | • Guidelines typically recommend routine dermatologic surveillance but no data on efficacy |

*Risk markedly higher for MLH1 and MSH2 carriers than for MSH6 or PMS2 carriers.  
**Aspirin use was associated with reduced risk of any Lynch-associated cancer.  
†Risk likely highest for MSH2 carriers.  
‡Most data suggest minimal increased risk compared with the general population.
Regardless of the test used, the underlying principle of universal tumor screening for Lynch syndrome is the same: (1) screen all patients with newly diagnosed colorectal and endometrial cancer for Lynch syndrome with one of these tumor tests; (2) follow up with MLH1 methylation analysis (with or without BRAF V600E mutation analysis in colorectal cancers) for MMR-D/MSI-H tumors with absent MLH1 and PMS2 expression; (3) refer the remaining patients to genetic counseling and confirmatory germline genetic testing in a CLIA-approved laboratory. Although universal tumor screening has been recommended by multiple professional organizations, a recent study found that only 28% of patients with colorectal cancer receive MSI or MMR IHC analyses at the time of diagnosis. This screening is becoming increasingly important, not only to identify patients who are more likely to have Lynch syndrome—which can help both the patient and their mutation-positive family members receive intensive cancer surveillance to prevent future cancers—but also to identify patients who are more likely to benefit from immune checkpoint inhibitor therapy.

High-Risk Clinic-Based Assessment for Lynch Syndrome
In addition to universal tumor screening for Lynch syndrome, it is still important that any and all individuals with suspicious clinical histories for Lynch syndrome receive genetic evaluation, even if they themselves have not yet been affected by cancer. There are various clinical tools available to help identify these patients quickly on the basis of personal and family history of cancer, including a validated three-question screen and the online PREMM5 prediction model. Patients who answer yes to any of the questions on the three-question screen or who are predicted to have a 2.5% or greater likelihood of Lynch syndrome on PREMM5 screening warrant referral for Lynch syndrome evaluation. In the past, when germline genetic testing was more expensive and less accurate, the cancer genetics clinic would have first recommended tumor screening for a patient with a family history of colorectal or endometrial cancer, and then would have proceeded to germline genetic testing only if a tumor was MMR-D. Because NGS germline testing panels are now widely available at much lower costs, it is generally cost-effective to order multigene panel testing on patients who are evaluated for Lynch syndrome or other hereditary cancer syndromes.

Data on such NGS germline panels are starting to emerge. In one study that examined a 25-gene panel of cancer susceptibility genes in individuals diagnosed with colorectal cancer before age 50, 16% of individuals harbored a pathogenic germline cancer susceptibility gene variant, only half of which were in Lynch syndrome genes. In another study that examined the same 25-gene panel in more than 1,000 individuals diagnosed with colorectal cancer across all ages, 9.9% carried a pathogenic germline variant in one or more cancer susceptibility genes, only one-third of which were in Lynch syndrome genes. Such studies have raised the question of whether all patients with colorectal cancer, or at least those diagnosed before age 50, should be offered germline genetic testing regardless of their tumor screening results. In addition, these studies suggest that testing should not be limited to Lynch syndrome genes but should include a broader pan-cancer panel of common hereditary cancer genes. It is always most informative to initiate genetic evaluation within a family for an individual affected by one of the cancers of concern, but such an approach often is not feasible for a wide variety of reasons. In such situations, germline testing performed on an at-risk unaffected individual with appropriate pre- and post-test counseling is a reasonable alternative.

IMMUNE-BASED THERAPIES FOR LYNCH SYNDROME–ASSOCIATED CANCERS
Although Lynch syndrome–associated colorectal cancers have superior prognoses, stage-for-stage, compared with their sporadic counterparts, some individuals with Lynch syndrome do unfortunately develop recurrent/metastatic colorectal cancer or other forms of advanced and incurable Lynch syndrome–associated cancer. Recent translational and therapeutic advances that leverage the immunologic effects of MSI that are classic for Lynch syndrome–associated cancers have resulted in dramatic changes to the treatment landscape for patients with Lynch syndrome who have advanced cancers (and individuals with non–Lynch syndrome advanced MMR-D/MSI-H cancers). MSI-H, by definition, is characterized by the somatic accumulation of small insertion or deletion events at repetitive stretches of DNA termed microsatellites. When such frameshift mutations occur at hotspot microsatellite loci within coding regions of tumor suppressor genes (e.g., TGFBR2), they act to promote carcinogenesis. However, these frameshift mutations can result in the accumulation of potentially antigenic frameshift neopeptides, which are thought to account for the tumor-infiltrating lymphocyte reactions that are classically seen in Lynch syndrome–associated (and other non-Lynch MSI-H) colorectal cancers.

The recent emergence of oncologic therapies such as immune checkpoint inhibitors that work through manipulation and upregulation of the patients’ own immune systems have exploited this underlying biology to create game-changing progress in the treatment of Lynch syndrome–associated (and other MSI-H/MMR-D) cancers. The most notable such therapeutic examples to date are monoclonal antibodies that target PD-1. In the first study to specifically examine such agents in metastatic, refractory MMR-D/MSI-H cancers, 11 individuals with MMR-D/MMI-H colorectal cancer, 21 individuals with MMR-proficient/microsatellite-stable colorectal cancer, and nine individuals with MMR-D/MMI-H noncolorectal cancers were treated with single-agent pembrolizumab. In this heavily pretreated cohort, there were markedly superior outcomes (hazard ratio for progression or death, 0.04; 95% CI, 0.01–0.21) in individuals with MMR-D/MSI-H cancers compared with those whose cancers were MMR proficient/microsatellite stable. By RECIST criteria, overall response rates were 40% and 71% for MMR-D/MSI-H
colorectal cancers and noncolorectal cancers, respectively, whereas there were no responses among those with MMR-proficient/microsatellite-stable colorectal cancers. Likewise, overall disease control rates were 90% and 71% for MMR-D/MSI-H colorectal cancers and noncolorectal cancers, respectively, compared with 11% for MMR-proficient/microsatellite-stable colorectal cancers. With a median follow-up time of 36 weeks, the median progression-free survival was not reached for either cohort of patients with MMR-D/MSI-H cancers (vs. a median progression-free survival of only 2.2 months among the patients with MMR-proficient/microsatellite-stable colorectal cancer).\textsuperscript{54} Follow-up data with pembrolizumab in 86 patients who had a wide variety of previously treated metastatic/advanced MMR-D/MSI-H cancers have shown an objective response rate of 53% (95% CI, 42%–64%) across tumor types, including a 21% complete response rate and a 77% overall disease control rate; median overall survival and progression-free survival had not been reached at a median follow-up time of 12.5 months.\textsuperscript{55}

A complementary single-arm phase II study examined nivolumab, another anti–PD-1 monoclonal antibody, in 74 individuals with chemotherapy-refractory MMR-D/MSI-H colorectal cancer.\textsuperscript{56} An investigator-assessed objective response rate of 31.3% (23 of 74 patients) was observed in this study, and the median duration of response was not reached during the study period (median follow-up time, 12.0 months).\textsuperscript{56} Likewise, the median overall survival was not reached during the study period, and the median progression-free survival was 14.3 months, which indicated that the responses experienced by patients with MMR-D/MSI-H colorectal cancer in this study were quite durable.\textsuperscript{56}

Data about the use of anti–PD-1 antibodies in advanced MMR-D/MSI-H cancers to date have not shown any significant difference in response rates or outcomes among individuals with known Lynch syndrome compared with those without Lynch syndrome.\textsuperscript{54,56} Correlative translational data\textsuperscript{59} have demonstrated marked expansion of T cells targeted toward frameshift neopeptides after treatment with anti–PD-1 antibody therapy in patients who experienced objective responses, which provides strong support to the hypothesis that these antigenic frameshift neopeptides are a fundamental factor underlying the success with immune-based therapies and which provides promise for strategies that likewise leverage immune-based mechanisms to prevent Lynch syndrome–associated cancers. Data are emerging about mechanisms underlying both primary and secondary resistance mechanisms to anti–PD-1 therapy as well, which suggests that\textit{β}-2 microglobulin mutations that lead to downregulation of antigenic presentation mechanisms may account for a sizeable fraction of resistance to immune checkpoint blockade.\textsuperscript{59}

These exciting successes led to the accelerated approval by the U.S. Food and Drug Administration of pembrolizumab to treat advanced, pretreated MMR-D/MSI-H cancer (regardless of primary site) and nivolumab (MMR-D/MSI-H colorectal cancer only) in 2017. Most recently, a single-arm phase II study of nivolumab with ipilimumab (a monoclonal antibody targeted against CTLA-4, another immune checkpoint protein) in 119 individuals with advanced MMR-D/MSI-H colorectal cancer demonstrated an overall response rate of 55% (with 83% of all responses lasting ≥ 6 months) and a 12-month overall survival rate of 85%.\textsuperscript{57} Such data suggest that there may be opportunities to synergize different mechanisms of immune checkpoint blockade with one another. Other ongoing clinical trials are examining the benefit of anti–PD-1 antibodies in the adjuvant treatment of resected stage III MMR-D/MSI-H colon cancers with and without chemotherapy (NCT02912559) and in the first-line treatment of metastatic MMR-D/MSI-H colorectal cancers (NCT02563002).

**Cancer Prevention in Lynch Syndrome: Colorectal Cancer**

Prospective data with long-term follow-up have demonstrated that frequent and early colonoscopic evaluation of healthy individuals with Lynch syndrome can significantly reduce colorectal cancer incidence, colorectal cancer–associated mortality, and overall mortality, thereby solidifying such screening as the core preventive intervention in Lynch syndrome.\textsuperscript{58} Recent data from a prospective multicenter European registry,\textsuperscript{59} however, have raised questions as to whether the preventive benefits of intensive colonoscopic surveillance with polypectomy might be overstated, in part because recent data suggest that some Lynch syndrome–associated colorectal cancers may develop as directly invasive malignancies rather than through the traditional adenoma–carcinoma pathway.\textsuperscript{60} Nonetheless, guidelines from ASCO, the European Society for Medical Oncology, the National Comprehensive Cancer Network, the U.S. Multi-Society Task Force on Colorectal Cancer, the American College of Gastroenterology, and others all consistently recommend colonoscopies every 1 to 2 years for healthy individuals with Lynch syndrome.\textsuperscript{3,7,42-44} Such guidelines mostly agree that the optimal age at which to begin colonoscopic screening is age 20 to 25, although data that demonstrate comparably lower rates of colorectal cancer for families with germline\textit{MSH6} and\textit{PMS2} variants (vs. those with\textit{MLH1} and\textit{MSH2} variants) have prompted some experts to suggest that later initiation of colonoscopies may be safe in this subset of individuals with Lynch syndrome.\textsuperscript{4,59}

Prophylactic colectomy is not considered a standard or necessary intervention for primary colorectal cancer risk reduction in individuals with Lynch syndrome, in large part because of the efficacy of colonoscopic surveillance.\textsuperscript{7,42,44} For individuals with Lynch syndrome who develop an early-stage colorectal cancer, however, the risk of metachronous colorectal cancer is particularly high if segmental resection is used to treat the index cancer (up to 62% at 30-year follow-up).\textsuperscript{61} Prospective registry data suggest that the risk of metachronous colorectal cancer can be reduced substantially by performing extensive colonic resection at the time of index colon cancer diagnosis (31% reduction in risk for every 10 cm of colon resected), although there is no
proven survival benefit to more extensive surgery. Thus, patient-specific factors, such as age, bowel function, comorbidities, compliance with screening, and patient preference, should all be taken into consideration to decide between segmental and more extended colonic resection for a Lynch syndrome–associated colon cancer.

**Endometrial, Ovarian, and Other Lynch Syndrome–Associated Cancers**

For women with Lynch syndrome, endometrial cancer and ovarian cancer represent the second- and third-most common associated malignancy, respectively, after colorectal cancer. Numerous studies have attempted to research the benefit of screening for endometrial and ovarian cancer in women with Lynch syndrome with techniques that include transvaginal ultrasonography, endometrial biopsies, and cancer antigen 125 (CA-125) tumor marker testing. Although such studies have shown some modest sensitivity for detection of endometrial carcinoma or endometrial hyperplasia with routine endometrial biopsies with or without ultrasonography, none of these screening techniques have consistently demonstrated high sensitivity to detect Lynch syndrome–associated endometrial or ovarian cancer, nor has such screening ever been shown to affect cancer incidence or mortality.

Compelling observational data have shown that risk-reducing surgery with hysterectomy and salpingo-oophorectomy have marked efficacy for prevention of endometrial and ovarian cancer in women with Lynch syndrome, although it remains unclear whether such surgery confers any actual survival benefit. Given the associated surgical risks as well as the associated psychological, cardiovascular, endocrinologic, skeletal, and sexual consequences of early-onset surgical menopause, however, it remains unclear as to how clinicians can best guide women with Lynch syndrome about the optimal timing of risk-reducing surgery. Furthermore, given the comparably lower risk of endometrial and ovarian cancers in women with *PM2* variants (and possibly *MSH6* variants), some have questioned whether risk-reducing surgery might be overtreatment for some women with Lynch syndrome. Despite these gaps in knowledge, most guidelines currently recommend consideration of risk-reducing hysterectomy and salpingo-oophorectomy at the completion of childbearing and/or in the early 40s, with consideration of annual transvaginal ultrasound and endometrial biopsy at age 30 to 35 (continued until risk-reducing surgery). Currently, there are no compelling data on effective screening for other Lynch syndrome–associated cancers, including gastric, urinary tract, pancreaticobiliary, small intestinal, or brain cancers. However, some guidelines recommend consideration of specialized screening in the setting of strong family histories of a particular cancer.

**Chemotherapeutic and Immune-Based Prevention**

Aspirin and other cyclooxygenase-2 inhibitors have long been suspected to have modest effects at reduction of the risk of colorectal cancer and adenomas on the basis of both observational data and various randomized prevention trials. To investigate whether such cancer-preventing benefits applied to patients with Lynch syndrome who have an inherently high risk of colorectal cancer, the international Colorectal Adenoma/Carcinoma Prevention Program 2 (CAPP2) study was launched in the late 1990s, for which individuals with Lynch syndrome were randomly assigned to receive 600 mg/day of aspirin or placebo (participants also were randomly assigned to take 30 g/day of resistant starch vs. placebo as a second intervention in this study). Although the first analysis after a mean of 29 months showed no significant difference in colorectal adenoma or carcinoma risk among those with Lynch syndrome in CAPP2 who received aspirin compared with placebo, a preplanned long-term analysis ultimately demonstrated a marked reduction in colorectal cancer incidence (incidence rate ratio, 0.37; 95% CI, 0.18–0.78) among participants who took aspirin for 2 or more years compared with those randomly assigned to placebo. Surprisingly, there was also a significant reduction in the incidence of any Lynch syndrome–associated cancer (incidence rate ratio, 0.59; 95% CI, 0.39–0.90) among participants who took aspirin for 2 or more years, which suggests that the preventive benefits may extend beyond the colorectum. On the basis of these compelling data, daily aspirin is now considered a standard component of Lynch syndrome cancer prevention, although the ideal dose and duration of use are as yet undefined. The ongoing CAPP3 study is examining 100 mg/day, 300 mg/day, or 600 mg/day of aspirin in a prospective, randomized trial of patients with Lynch syndrome. Interestingly, a subgroup analysis of CAPP2 participants found that obesity was associated with an increased risk of colorectal cancer and also suggested that the preventive benefits of aspirin in Lynch syndrome may be limited to obese individuals. Additional studies are needed to better clarify the interplay among aspirin, obesity, and dietary/lifestyle factors on cancer risk in Lynch syndrome. Various observational data have suggested potential cancer-preventing benefits from ibuprofen, calcium supplementation, and multivitamin use to reduce colorectal cancer risk in individuals with Lynch syndrome, although such interventions should not be considered standard in the absence of confirmatory prospective randomized clinical trials.

Various studies also have examined the potential preventive benefits of exogenous hormone use to reduce the risk of endometrial cancer in women with Lynch syndrome. In one large observational study, use of hormonal contraceptives for 1 year or more was associated with a significantly reduced likelihood of endometrial cancer (HR 0.39; 95% CI, 0.23–0.64) in women with Lynch syndrome. The same study also showed a mildly reduced likelihood of endometrial cancer in the setting of nulliparity and earlier onset of menarche. Confirmatory prospective data about the preventive effects of hormonal factors in Lynch syndrome–associated endometrial cancer incidence are lacking, though one small prospective biomarker study demonstrated that progestin-containing oral contraceptives and...
Depo-medroxyprogesterone acetate use resulted in significantly reduced endometrial proliferation in pre- and postintervention biopsies.\textsuperscript{72}

As outlined in this article, the phenomenon of MSI-H, which is a hallmark of Lynch-associated cancers, results in the accumulation of frameshift mutations at known microsatellite loci scattered throughout the coding and noncoding regions of the tumor genome.\textsuperscript{52} The predictable nature of such frameshift mutations and their associated neopeptides has led to great interest in the notion of leveraging immune-based methods, such as vaccines, for primary prevention of Lynch syndrome–associated cancers.\textsuperscript{73} Curiously, data have shown that healthy, cancer-free individuals with Lynch syndrome harbor circulating T cells that are reactive to such MSI-induced frameshift neopeptides, although they have never had a detectable cancer; this strongly suggests that innate immunosurveillance mechanisms already play a role in suppressing MSI-induced carcinogenesis in such individuals.\textsuperscript{74} Nonneoplastic colonic crypts from healthy Lynch syndrome carriers have been shown to demonstrate MMR-D by IHC and MSI-H by PCR, which leads to the intriguing hypothesis that the healthy colon of patients with Lynch syndrome is itself a key source of immunogenic frameshift neopeptides that serve to autovaccinate such patients and suppress MSI-induced carcinogenesis.\textsuperscript{75} A more precise understanding of the mechanisms by which Lynch syndrome–associated carcinogenesis escapes immune surveillance will be key to help leverage such discoveries into immune-based cancer prevention.\textsuperscript{52,76}

**CONCLUSION**

The identification and management of individuals and families with Lynch syndrome has evolved rapidly during the past decade or so. Advances in molecular testing and NGS technologies now allow all patients with colorectal and endometrial cancers to reliably receive screening for underlying Lynch syndrome, whereas innovations in immuno-oncology promise to continue revolutionizing the treatment of Lynch-associated cancers. To continue moving the needle forward, expanded efforts to diagnose Lynch syndrome in healthy, cancer-free individuals are needed, rather than relying on the identification of Lynch syndrome through a new cancer diagnosis. Identification of Lynch syndrome offers the potential to prevent cancer-related morbidity and mortality, and continued progress in understanding the immune system’s ability to recognize, eradicate, and intercept Lynch-associated neoplasia offers many intriguing possibilities for immune-based primary cancer prevention.

### References


CARE DELIVERY AND PRACTICE MANAGEMENT
The benefits of outpatient palliative care to patients with cancer are well established.1-4 Although the prevalence of outpatient palliative care services in cancer centers has increased,5,6 many oncologists who practice in rural or community settings have limited access to palliative care specialists. The data about successful models of outpatient palliative care are still emerging.7 Successful community-based outpatient practices must demonstrate financial responsibility and must improve clinical outcomes. Although community-based oncology practices function largely in a setting in which fee-for-service is a critical contributor to the financial health of the practice, most palliative care services featured in the literature originate in academic centers or integrated health systems and are supported with a combination of research dollars, philanthropy, or a model of care not reliant on fee-for-service for income. This article reviews key considerations for how to build an outpatient palliative care program:

1. Define the scope and benefits of outpatient palliative care.
2. Identify strategies to overcome common barriers to integrating outpatient palliative care into cancer care.
3. Outline a business case for outpatient palliative care.
4. Describe successful models of outpatient palliative care highlighted in the literature.
5. Examine important factors for design and operation of a palliative care clinic.

DEFINING PALLIATIVE CARE AND ITS BENEFIT TO COMMUNITY ONCOLOGY

An accurate definition among oncology clinicians, patients, and caregivers is necessary to overcome barriers to palliative care referral. According to ASCO, palliative care is designed to improve the QOL of patients and families living with cancer by addressing patients’ pain, symptoms and functional limitations, communicating about prognosis, assessing illness understanding, clarifying treatment goals, providing support for coping with serious illness, and assisting with transitions in care. Palliative care should be provided by an interdisciplinary team.8

In the oncology setting, palliative care can be used at any stage of illness and can be provided concurrently with curative or disease-modifying cancer therapies.8 In fact, ASCO, the European Society of Medical Oncology,9 the Society of Gynecologic Oncology,9 and the American Academy of Pediatrics10 all recommend early use of palliative care concurrent with disease-modifying cancer treatment for patients living with cancer. For patients with advanced cancer, evidence suggests that earlier referral in the outpatient setting is important to improve quality-related outcomes, including...
end-of-life hospitalization, emergency department use, hospice use, and intensive care unit stays, to reduce cost of care, and to improve patients’ physical and emotional symptoms. Decreased caregiver distress is also a documented outcome of early palliative care.

**Indications for Early/Outpatient Palliative Care Referral**

Despite lack of evidence to define the most appropriate reasons for outpatient referral, a recent Delphi process that involved international palliative care and oncology experts led to the development of need- and time-based indications for outpatient referral. Indications are listed in the Sidebar.

**PRACTICAL APPLICATIONS**

- Well-designed, randomized trials demonstrate the benefit of integrating palliative care into cancer in the outpatient setting and early in the cancer care trajectory.
- Patients and oncologists often mistakenly equate palliative care with end-of-life care, which leads to delayed referrals and missed opportunities for patients.
- A palliative care team embedded into an oncology clinic allows joint visits with patients, which may enhance the prognostic awareness of patients and facilitate informed decision making.
- By aligning with institutional goals, such as reduction of re-admissions or unnecessary health care use at the end of life, programs can make a strong fiscal case for outpatient palliative care clinics.
- Effective palliative care team has a distinct, complementary, and collaborative role with oncology teams in the care of patients with cancer.

**FACILITATORS AND BARRIERS TO PALLIATIVE CARE REFERRAL**

**Patient and Family Facilitators and Barriers**

A public opinion survey established that few people understand what palliative care is. However, when appropriately educated about the services provided, most people would be willing to have palliative care for themselves or a loved one with serious illness. Studies of patients with cancer suggest that many initially associate palliative care with hospice and death and/or dying. Patients may associate palliative care referral with decreased hopefulness or choice about their care. Notably, those who received early integrated palliative care reported that their initial concerns were replaced by appreciation for the QOL benefits associated with palliative care services and recognition that services provided by palliative care teams and oncologists were distinct but complementary. Even after they understood the value, patients still recommended calling palliative care services by a different name.

**Branding/naming.** Given that palliative care grew out of the hospice movement and that many providers and patients associate it with death, dying, or hospice services, some have advocated renaming these services to remove the associated stigma. The most frequently suggested alternative is supportive care. At The University of Texas MD Anderson Cancer Center, oncologists and advance practice providers preferred supportive care, and renaming the service resulted in increased referrals. Other practices avoid the problematic terms by being named in honor of philanthropic donors or by using a name that is descriptive of services (e.g., the Symptom Management Service).

**Oncologist Facilitators and Barriers**

Reasons oncologists refer patients for palliative care. Studies to explore facilitators and barriers to referral among oncologists suggest that individual factors may affect referral more than institutional bias for or against palliative oncology care. Multiple studies suggest that oncologists are most likely to refer for assistance with complex pain and symptom management and less likely to solicit help with goals of care. Completion of a specialty palliative care rotation during training increased likelihood of referral, as did adequate access to palliative care services in one’s institution. However, numerous attitudinal, educational, and structural barriers exist.

**Attitudinal barriers.** Multiple studies indicate that oncologists incorrectly link palliative care with death, dying, hospice, or end-of-life care, and some believe it should be offered only when there are no more cancer-directed therapies available. Some physicians may be resistant to changing this belief. Attitudinal barriers toward palliative care expressed by oncologists include the following:

- Persistent association with death, dying, hospice, and/or end-of-life care
- Stigma associated with the name "palliative care" and concern that patients may have negative associations
- Belief that palliative care is an alternative to oncology

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**SIDEBAR. List of Referral Indications for Outpatient Specialty Palliative Cancer Care**

1. Severe physical symptoms
2. Severe emotional symptoms
3. Request for hastened death
4. Spiritual or existential crisis
5. Health care decision making/goals of care/advance care planning
6. Patient request
7. Delirium
8. Neurologic complications of cancer: brain or leptomeningeal metastases, spinal cord compression/cauda equina syndrome
9. Within 3 months of diagnosis with advanced/metastatic cancer with a median survival < 1 year
10. Diagnosis of advanced cancer with progression despite two lines of systemic therapy

Adapted from Hui et al.
care or is not compatible with concurrent aggressive anticancer care
• Oncologist distrust of palliative care providers; belief that certain topics, such as prognosis or goals of care, are the sole domain of oncology clinicians
• Belief that patients/families will feel abandoned or have less hope if their oncologist refers them to palliative care
• Fear of upsetting other oncology multidisciplinary team members (e.g., medical oncologist upset that radiation oncology colleague involves palliative care team)
• Belief that academic palliative care models don’t translate well into community settings

Primary versus specialty palliative care in oncology practice. Practicing oncologists often say, “But I do palliative care!” This belief may be another barrier to palliative care referral.31,35 Indeed, many oncologists are skilled at management of cancer-associated pain and symptoms, as well as discussion about prognosis and goals of care. These are essential elements of primary palliative care.34 However, most oncologists do not have specialized training to address more complex symptomatic or emotional needs of patients and families,37-41 and many may not have time during routine office visits to address broader psychosocial issues related to suffering and coping that affect patients with cancer and their families. A 2016 joint guidance statement by ASCO and the American Academy of Hospice and Palliative Medicine identified basic symptomatic assessment and management skills, as well as elements of end-of-life care and communication, that were essential aspects of high-quality primary palliative care for patients with cancer. However, expert consensus was that some domains require specialist intervention.42 The degree to which an individual oncology clinician feels they can provide primary palliative care may depend on many factors, including their training, continuing education, attitudes, and practice environment. Professional organizations recommend that oncologists receive palliative care training in graduate and continuing education environments to develop and refine their skills.9,43

Structural Barriers to Outpatient or Community-Based Palliative Care
Outpatient and community-based palliative or supportive oncology programs have the benefit of providing care in the same location that most patients with advanced cancer receive their oncology care—in the outpatient setting. Although 90% of U.S. hospitals with more than 300 beds provide services,30 and although many patients at American and European comprehensive cancer centers have access to outpatient palliative care,6,44 widespread access outside of large academic centers to outpatient or community-based palliative care for patients with cancer may be limited.3,45

Surveyed oncologists reported the following structural or financial barriers to outpatient or community-based specialty palliative care referral32,29,31,46:
• Lack of service availability
• Lack of timely access for referred patients
• Lack of awareness about outpatient or community-based services
• Location of palliative care clinics off site/away from oncology clinics
• Practice environments in which palliative care clinics only accept patients who are not receiving cancer-directed therapies
• Concern about copays and reimbursement for palliative care services

Successful community-based outpatient palliative care clinics will anticipate and address many of these concerns.

BUILDING A BUSINESS PLAN FOR YOUR PALLIATIVE CARE CLINIC
Outpatient palliative care offers tremendous value not just to patients with cancer, families, and clinicians, but to institutions as well. Palliative care supports high-quality clinical care, including improved symptom control and, in some instances, reduced mortality.1,47 These clinical benefits are at the core of guidelines and recommendations from national and international oncologic organizations.8,48-51 ASCO first recommended palliative care for all patients with serious symptoms or metastatic disease in 201249 and reaffirmed their recommendations in 2016.8

Notably, this clinical (or moral) imperative (i.e., provide palliative care because it is the right thing to do for patients) is aligned with a financial imperative: palliative care results in important cost avoidance and cost savings in the context of a global care budget. Palliative care outpatient work typically includes a robust interdisciplinary team (including providers such as chaplains and social workers who typically cannot bill insurance for their work) and extensive phone and follow-up support after scheduled clinic visits. As such, palliative care physician and nurse practitioner billing typically is not adequate to support comprehensive outpatient services in a fee-for-service system.52 However, with the goal of making patient care consistent with patient wishes, palliative care often results in provision of more desired services that usually are not very expensive (e.g., symptom management, home care, and hospice), but fewer unnecessary services that usually are very expensive (e.g., end-of-life hospitalizations, intensive care, and chemotherapy). In balance, with a global budget in mind, outpatient palliative care is associated with fewer costs for institutions that bear global (at-risk) costs of care.53,54 The cost savings associated with less unnecessary health care use at the end of life (e.g., emergency department visits, hospitalizations, intensive care unit stays in the last days/months) and earlier hospice referral justifies the costs of early, integrated outpatient palliative care services for patients with cancer.

Across the country, institutions that provide cancer care are recognizing the possibilities for expanded outpatient palliative care services to achieve the triple aim: improvement for the patient (and caregiver) experience, improvement in the health of populations, and reduction of per capita cost of health care.55 The movement to establish value-based care has created an historic alignment among
what patients, families, health care clinicians, and health care institutions want. This alignment likely explains some of the observed growth in palliative care services in cancer centers. Nationally, cancer centers are developing and growing outpatient palliative care services. The vast majority of National Comprehensive Cancer Network–member institutions now offers outpatient palliative care and provides an average of 469 consults per year, staffed by an average of 6.8 full-time equivalent personnel.6

Without adequate explicit reimbursement (i.e., billing income) for services to create a flow of new monies that is obviously visible to cancer center and practice administrations, palliative care programs must engage cancer centers and practices by presenting their value argument clearly and in terms that matter to the institution.10 Palliative care must align with the cancer center or practice and demonstrate the financial case for their comprehensive program. Such an argument can include data of cost savings published in the peer-reviewed literature. Although the published data have distinct limitations and some inconsistencies, studies of home-based and clinic-based community palliative care demonstrate important clinical and financial benefits.1,12,47,56-64

Early referral and palliative care early in the course of cancer care appear to be key.11-13,65

However, nearly every institution wants their own local, not national, data. Palliative care departments must project the cost savings associated with performance at their own institution's own mission statement, values, strategic initiatives, language, and data. Palliative care groups must engage cancer centers and oncology clinics (e.g., cost avoidance from reduced health care use, quality improvement) or payer or market forces within health care systems may generate more support for outpatient programs.

As an example of mission alignment and data that support the business case for outpatient palliative care, the outpatient palliative care team at the UCSF Helen Diller Family Comprehensive Cancer Center (called the Symptom Management Service) generated data to describe the improved end-of-life health care use for cancer center decedents seen by palliative care late in their care (fewer than 3 months before death, typically seen by the inpatient palliative care service) compared with early (more than 3 months before death, typically seen by the outpatient palliative care service).12 These data showed improved end-of-life health care use (i.e., fewer hospitalizations, emergency department visits, in-hospital mortality, 30-day mortality, and death within 3 days of hospital discharge) for early palliative care. This was associated with an attenuation of the typical increase in health care costs at the end of life and a savings per patient of approximately $5,000 (accounted for by savings in inpatient expenses). In the setting of inadequate national data to benchmark staffing for outpatient palliative care, such utilization/cost data, along with quality data, contributed to leadership support for the request to expand the work of non-billing palliative care team members, including an additional nurse and administrative assistant, in the outpatient setting. Additional social work support is being considered.

Some palliative care teams may have the ability to construct a robust business plan that is based on health care value, but many will need the support of the institution (i.e., finance and data personnel) or consultation from outside experts. Since 2003, through their Palliative Care Leadership Center initiative (of which M. W. R. is a founding member), the Center to Advance Palliative Care has offered strategic consulting and mentoring to new or growing programs across the country and has developed a recent initiative focused on community-based palliative care.

To develop a robust and sustainable outpatient palliative care service, numerous strategic considerations are important. Each of these has implications for staffing, clinical capacity, and health care finances that each program must consider. Strategic elements to consider include the following:

- Model of practice (clinic-based [stand-alone or colocated] or home-based)
- Scope of your practice (What will your service do? What patients will you see? What patients will you not see?)
- Level of responsibility (consultation only, comanagement, or primary care)
- Referral process
- Visit specifics (length of visit for new patients and follow-up visits, as well as for family meetings, advance care planning sessions)
- Telemedicine capabilities
- Visit volume
- Mechanism for discharging patients from the practice
- Strategies for quality maintenance and improvement (including patient-reported and other data, data and reporting management systems)
- Clinical care space
- Staffing (What disciplines will be involved? Will they be palliative care certified? Where do they “live” administratively?)
- 24/7 coverage
- Record-keeping and electronic medical record capabilities
- Billing processes
- Communication and coordination with oncologists and referring providers
- Opioid management (prescribing, use, and monitoring)
- Service staff sustainability and resiliency

Notably, the program design that is right for any one institution is the one that is fitted to that institution’s clinical needs and strengths, culture and environment, and payment model.

KEY CONSIDERATIONS IN DEVELOPING A PALLIATIVE CARE CLINIC

Model/Location of the Clinic

Independent clinic. In an independent (i.e., stand-alone) clinic model, the palliative care and oncology clinics are separate in location and usually in funding. Appointments are...
not linked with oncology appointments, though efforts can be made to coordinate scheduling according to the availability and flexibility of both the oncologist and the palliative care clinic staff. All the clinic staff, including the receptionist, medical assistant, and after-hours coverage, are the responsibility of the palliative care team, and this responsibility assignment has implications for the cost of the clinic. Independent clinics have the advantage of creating a separate environment and are able to manage visits with multiple members of the interdisciplinary team.

**Embedded or colocated.** Palliative care clinics that aim to serve patients with cancer primarily or exclusively are commonly colocated along with the oncology clinic in the cancer center, and degrees of integration or embeddedness—collaborative activity and program services—vary. Typically, either a physician or a nurse practitioner, sometimes with support of social work,7 coordinates with the oncologist to see patients in tandem with them. A key feature of an embedded clinic is the opportunity for the oncologist and the palliative care clinician to discuss patient issues in real time, which ensures that the palliative care clinician understands the prognosis and anticipates the next steps with respect to treatment, and which ensures that the oncologist understands recommended symptom management and psychosocial interventions. Critical information may be conveyed during joint visits, which ensures a consistent message to the patient and family. The model also facilitates education and support from palliative care to oncology and the reverse.66

Although strong data compare concurrent outpatient palliative care to usual oncologic care,1-3,12,14 little data test the relative impact of different models to deliver palliative care on outcomes. Einstein at al67 compared outcomes of decedents with access to an embedded palliative care model with those who had access to an independent palliative care clinic. Findings included earlier integration of palliative care as part of the oncology visit...
TABLE 1. Overcoming Barriers and Obtaining Buy-In for Outpatient Palliative Care

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Buy-In Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assess Practice and Market Forces</strong></td>
<td>Define your oncology practice’s PC resources and needs:</td>
</tr>
<tr>
<td></td>
<td>• Who are the provider, patient, health system, payer, and community stakeholders?</td>
</tr>
<tr>
<td></td>
<td>• Identify institutional PC champions</td>
</tr>
<tr>
<td></td>
<td>• Identify knowledge, attitudinal, and service/access barriers to PC integration</td>
</tr>
<tr>
<td></td>
<td>• Identify local PC/supportive care providers and hospices</td>
</tr>
<tr>
<td></td>
<td>• Inquire about potential collaborative service models</td>
</tr>
<tr>
<td></td>
<td>• Identify existing local/regional resources and services</td>
</tr>
<tr>
<td><strong>Evaluate Potential Models for Care</strong></td>
<td>Consider what kind of oncology-PC partnership may meet your practice’s service needs:</td>
</tr>
<tr>
<td></td>
<td>• Embedded clinic: may improve oncologist–PC communication and ease of access for patients</td>
</tr>
<tr>
<td></td>
<td>• Independent PC clinic: less risk for oncology practice, but may decrease opportunities for collaboration and may limit access for patients</td>
</tr>
<tr>
<td></td>
<td>• Home-based PC programs: meets patients in home settings, but may decrease face-to-face contact between oncology and PC providers; less data to support model specific to cancer</td>
</tr>
<tr>
<td></td>
<td>• Telehealth model: telemedicine or telephonic care management models may be useful in rural or resource-poor environments, or in settings with limited PC provider capacity15,73,74,80</td>
</tr>
<tr>
<td></td>
<td>• Primary PC model: with the TEAM approach to improve primary PC capacity, draws from literature on best practices but needs validation in trial setting69</td>
</tr>
<tr>
<td><strong>Define Consultation Etiquette and Expectations for Collaboration</strong></td>
<td>Collaborate with PC partner for the following:</td>
</tr>
<tr>
<td></td>
<td>• Define referral pathways and processes</td>
</tr>
<tr>
<td></td>
<td>• Consider suggested clinical criteria for referral, including automatic triggers</td>
</tr>
<tr>
<td></td>
<td>• Define expectations for timely patient referral and urgent access</td>
</tr>
<tr>
<td></td>
<td>• Consider early consultations for pain and symptom control to integrate and normalize PC team in patient care model81</td>
</tr>
<tr>
<td></td>
<td>• Clarify bidirectional communication expectations between oncologists and PC providers</td>
</tr>
<tr>
<td></td>
<td>• Clearly define roles among oncology and palliative team members31</td>
</tr>
<tr>
<td><strong>Identify PC Liaison or Champion in Your Oncology Setting</strong></td>
<td>Identify a PC liaison or champion in your practice (e.g., navigator, case manager, nurse, advance practice provider)32</td>
</tr>
<tr>
<td></td>
<td>• Establish a model for shared staffing with palliative-trained interdisciplinary team members (e.g., social workers, chaplains, nurses, advance practice providers)35</td>
</tr>
<tr>
<td></td>
<td>• Provide continuing education to practice liaison to build their PC skill set</td>
</tr>
<tr>
<td></td>
<td>• Invite PC providers to tumor board</td>
</tr>
<tr>
<td><strong>Educate Providers on the Brand, Messaging, and Services</strong></td>
<td>Provide oncology clinicians with regular opportunities to attend primary PC continuing education</td>
</tr>
<tr>
<td></td>
<td>• Clearly define PC services and delivery models</td>
</tr>
<tr>
<td></td>
<td>• Develop scripting to introduce PC effectively to patients/families and to limit the stigma85</td>
</tr>
<tr>
<td></td>
<td>• Identify a patient’s PC service needs or goals (e.g., pain, symptom control, advance care planning) and frame your recommendation for PC referral on the basis of those perceived needs83</td>
</tr>
<tr>
<td></td>
<td>• Example: “Your pain has been difficult to manage, and I’d like to refer you to a team of experts who can work with me to get it under better control.”</td>
</tr>
<tr>
<td></td>
<td>• Avoid language associated with hospice, death, or dying in descriptions of PC, and avoid describing PC as a service for patients with cancer for use “when there is nothing more we can do”</td>
</tr>
<tr>
<td></td>
<td>• Consider naming services, such as supportive care or supportive oncology, or consider using a descriptive name, such as symptom management service, rather than PC25,27,84</td>
</tr>
<tr>
<td></td>
<td>• Normalize early PC referral81,82: “This is the way we always do it.”</td>
</tr>
<tr>
<td><strong>Align Service Delivery and Marketing With the Needs of Patients/Families</strong></td>
<td>Clearly define your PC program by using language that facilitates patient understanding86:</td>
</tr>
<tr>
<td></td>
<td>• Naming: consider supportive care or other non-PC names</td>
</tr>
<tr>
<td></td>
<td>• Message: create a symptom- and quality of life–oriented message; avoid focus on end-of-life care</td>
</tr>
<tr>
<td></td>
<td>• Service delivery model: attempt to provide PC services by using a model that addresses the needs of your population (embedded vs. independent vs. other)</td>
</tr>
<tr>
<td></td>
<td>• Provide educationally appropriate marketing materials for patients and families</td>
</tr>
</tbody>
</table>

Abbreviations: PC, palliative care; TEAM, Time Education standardized Assessment and interdisciplinary Management.
care services and longer hospice enrollment for those with access to an embedded model. Notably, the referring oncologists were the same for both groups. This suggests that the embedded model may be effective to overcome certain barriers. Certainly, the incorporation of a palliative care clinician into the oncology team sends a strong message to patients and families that it is part of usual cancer care. Effective embedded clinics require substantial buy-in from at least one oncologist in the practice to be successful.

Method for Referral: Triggered Versus Physician Discretion

In traditional clinical practice, referral to another specialty relies on the discretion of the referring physician. Many health care professionals equate palliative care with end-of-life care, which leads to late referrals. The eligibility criteria of the clinical trials of outpatient palliative care effectively served as a trigger for the intervention arm, whereas referrals to palliative care were at physician discretion in the usual-care arm. Such triggers consistently result in earlier involvement of palliative care and improved outcomes. The criteria were largely based on diagnoses (e.g., a diagnosis of an advanced cancer) that portend limited prognoses. In some cases, a symptom severity score greater than a certain cutoff served as a trigger for a referral.

Implementation of a trigger outside of a trial requires buy-in from key members of the oncology team who are expected to refer, as well as the palliative care team. In our experience, oncologists were able to agree on pre-specified criteria in the abstract, yet frequently would not refer patients who met those criteria unless informed that the patient met the trigger. Identification of patients who meet prespecified criteria involves screening charts in advance, which requires additional staffing, which may not be feasible for all clinics. In addition, such screening is likely to enhance referrals. This may be an effective strategy for clinics seeking to expand their volume, but a more measured approach may be considered in clinics already at capacity.

Staffing Considerations

Palliative care, by definition, is delivered by an interdisciplinary team. The most common members include physicians, nurse practitioners, social workers, and nurses. Some teams also include a chaplain, psychologist, pharmacist, or dietician. When an independent clinic is designed, the needs of the patients and providers being served may determine the composition of the interdisciplinary team.

When palliative care is embedded into a cancer team, it may be impractical to bring a full interdisciplinary team to every patient visit. Also, the oncology team may already include members of different disciplines, such as a nurse or social worker. By building close relationships with all members of the oncology team and by avoiding redundancy, a single palliative care clinician may incorporate into a larger interdisciplinary cancer care team to deliver effective outpatient palliative care services. This model has financial advantages, because the palliative care clinician can generate revenue and because the cost of the other providers as well as the administrative and support staff comes out of the cancer clinic. This hybrid model recognizes the key elements of palliative care identified in the Time Education standardized Assessment and interdisciplinary Management (TEAM) approach, and it includes one individual with specialized training. (Please see the subsection "Other alternatives: Enhanced primary palliative care" for expanded discussion of the TEAM approach.) Alternatively, members of a specialty palliative care interdisciplinary team can see the patient serially, as necessary, and incur greater costs but avoid the logistical challenge of a large team that sees the patient in a small office.

Medication Management

Prescribing practices vary in palliative care clinic settings. The decision to prescribe means that the team is assuming responsibility for managing medications, adverse effects, adjustments, refills, and increasingly onerous regulatory paperwork. Some clinics, recognizing the limitations of their staff and/or the inability to provide off-hours coverage, opt to defer prescribing and what accompanies it to the primary team. This approach puts less burden on staff and may encourage more learning opportunities for the referring provider. This approach also carries a risk that recommendations may not get implemented. When oncology and palliative providers collaborate for patient care, clear roles about prescription management should be defined to avoid mistakes or misunderstandings.

OVERVIEW OF SOME SUCCESSFUL MODELS IN THE LITERATURE

A successful palliative care outpatient model will take into account the needs and concerns of the patients, the referring oncology specialists, the collaborating providers, and the practice environment into which it is being integrated. This is not meant to be a comprehensive list, but a review of the literature. The following examples of clinic models with published evidence of benefit highlight different effective programmatic features.

Traditional Clinic-Based Oncology–Palliative Care Collaborations

Example 1: Palliative care in academic oncology practice (colocated model). The work by Temel et al drew attention to outpatient palliative care because it demonstrated improvements not only in QOL but also in a substantial survival advantage. In this study, conducted at a major academic medical center, patients with non–small cell lung cancer who were randomly assigned to the intervention saw a single palliative care physician or nurse practitioner on a monthly basis within 8 weeks of diagnosis. Visits generally were timed to coincide with their scheduled oncology physician or treatment visits. Palliative care clinicians
addressed symptoms, coping, and illness understanding with equal frequency at all visits. Other content of these visits varied during the illness trajectory; early visits focused on building rapport with the patient, establishing information preferences and prognosis awareness, and discussing cancer treatment and adverse effects. Issues related to end-of-life care preferences were not addressed until later in the relationship.71 This model has been replicated elsewhere, including with an interdisciplinary team.

Colocated or embedded models have the perceived benefit of increased direct collaboration, education, and communication between oncologic and palliative care providers about patient care, and they provide joint visits for patients with the oncologist and the palliative care specialist. Many oncologists note a preference for embedded models of care for this reason.28,31,35 In addition, these models directly connect three important stakeholders: patients/families, oncologists, and palliative providers (Fig. 1).

Example 2: Palliative care in a private oncology practice.

In a similar delivery model, Muir et al59 embedded a hospice-employed palliative care clinician and a fellow in a half-day palliative care clinic in a busy private oncology practice. The hospice and oncology practice had a longstanding collaborative relationship. Referring oncologists from the group could make referrals for limited consultation for a problematic symptom or extensive consultation, which would include discussion of goals of care and possibly referral to hospice, if appropriate. The palliative care clinicians respected the scope of the oncologist’s referral. Clearly defining and respecting the scope of the referral are examples of appropriate consultation etiquette that addressed one reported barrier to referral from the literature.29,32,35

Referrals were tracked and compared the practice where the palliative care clinic was embedded among oncologists who also received education with an affiliated group that received education and with nonaffiliated practices without the education; all practices could refer to the palliative care clinic for consultation. After the pilot, referrals increased dramatically both to the clinic and to the inpatient palliative care service at the affiliated hospital. Not surprisingly, the most dramatic increase was from oncologists who had access to the embedded model. Data collected from a subset suggested that symptom burden improved in those seen in the palliative care clinic more than once. Opioid-prescribing practices also improved.72 Satisfaction, measured by anonymous survey of the referring providers, was high.

In an effort to demonstrate how this model aligned with the goals of the private practice oncology group, the authors hypothesized that the time spent by palliative care clinicians in the course of all their consultations was time that oncologists would have spent with these patients had the palliative care clinic not existed. According to this premise, they estimated that each referring oncologist saved an average of 170 minutes per patient referred. For practices in which there is a wait to see new patients, this could be a potent argument to support availability of a palliative care clinic.

Alternative Models for Oncology–Palliative Care Collaboration

Example 3: Telehealth palliative care support.

In the first two examples, palliative care specialty clinicians made themselves available in the same space and often on the same day as the oncologists who would refer. In a third model, Education, Nurture, Advise Before Life Ends (ENABLE), palliative care was provided with one face-to-face visit followed by four weekly psychoeducational phone sessions from trained advance practice nurses and then monthly sessions for the duration of the study.3,4 Patients in the intervention showed improvement in mood, a trend toward symptom improvement, and no change in health care use. This nurse-led telephonic model—an example of a tele-health intervention—has advantages in rural settings, where regular palliative care clinic visits may not be feasible, and offers a substantial impact from a relatively simple intervention. This work was funded by a research grant. Although reimbursement for virtual encounters is evolving and parity legislation is widespread, this model may pose challenges in a community practice in which billing would be expected to fund much of the work of a palliative care clinician.

Additional teledicine models of clinical palliative care service delivery to patients with cancer via video or telephonic methods exist, and they offer promising but mixed results related to overall symptom and service benefits.73–75 The Project Extension for Community Healthcare Outcomes (ECHO) model, which uses technology to deliver primary palliative care education to frontline providers in varied settings, is also described in the literature, although data are limited about its clinical impact on patients.76 Given the workforce and geographic limitations that affect palliative care, telemedicine models hold promise, but additional research is needed.

Example 4: Home-based palliative care.

Patients with advanced cancer may face challenges in access of care in clinic settings because of physical, functional, or resource-based limitations. Home-based palliative care may offer a solution for patients with cancer, and this model has been explored with some success in cancer and mixed patient populations.61,77 However, additional research is needed to determine the best models for home-based palliative care and oncology collaboration.

Other alternatives: Enhanced primary palliative care.

In environments with limited access to resources (i.e., rural, underserved regions or regions with limited oncology and palliative care staffing) or insurmountable barriers to palliative care integration, oncology practices might adopt key elements from the published trials about concurrent palliative and oncology care and implement them in a limited manner.69 The TEAM approach advocates for time (an additional hour per patient per month), patient-focused education, standardized assessments (e.g., routine symptom assessment with standardized tools), and interdisciplinary
management protocols to incorporate primary palliative care for patients with cancer. Because a benefit of palliative care is the interdisciplinary support for patients and families, the TEAM model advocates building relationships with interdisciplinary team members, such as advance practice providers, chaplains, and/or social workers, as an extension of the oncology team. The TEAM approach articulates critical components of palliative care and suggests a practical means of delivering them. Additional study and more approaches that are less revenue intensive, such as CONNECT (i.e., care management by oncology nurses to address supportive care needs), are needed to see if these approaches yield the same benefits of established models.

STRATEGIES FOR PROGRAM DEVELOPMENT

Table 1 lists strategies that are culled from literature as well as expert opinion. These include approaches to overcoming common hurdles and ways to obtain buy-in for building outpatient palliative care programs. Additional research is needed to establish innovative models of care and expand upon those mentioned here.

CONCLUSION

Outpatient palliative care programs provide substantial benefits to patients and their caregivers. Designed properly, they can also support oncologists in some of their most challenging work. Unlike so many other new oncologic advances, palliative care extends survival and enhances QOL and quality of care while it reduces costs. A recent study of high-value oncology practices named early and normalized palliative care as one of the three attributes with the highest potential to lower cost and at the same time maintain a high quality of care. More examples of innovative, efficient, and practical implementation of outpatient and community-based palliative care are needed in the literature so that we can learn from each other’s experiences. Improved integration of palliative care into community-based oncology practice represents an enormous opportunity to comply with the ASCO recommendations for the benefit of those whom we serve—to simultaneously enhance the experience of patients and families with advanced cancer and curb health care expenditures, a rare alignment of clinical and fiscal goals.

References


Implementation of Patient-Reported Outcomes in Routine Medical Care

Ethan Basch, MD, MSc, Lisa Barbera, MD, Carolyn L. Kerrigan, MD, MHCDS, and Galina Velikova, MD, PhD

OVERVIEW

There is increasing interest to integrate collection of patient-reported outcomes (PROs) in routine practice to enhance clinical care. Multiple studies show that systematic monitoring of patients using PROs improves patient-clinician communication, clinician awareness of symptoms, symptom management, patient satisfaction, quality of life, and overall survival. The general approach includes a brief electronic survey, administered via the Web or an app or an automated telephone system, with alerts to clinicians for concerning or worsening issues. Patients have generally been asked to self-report on a regular basis (remotely between visits and/or at visits), with reminders prompting patients to self-report that are sent via email, text, or automated phone message. More recently, care management pathways for patients and clinicians have been triggered by PRO system alerts. PRO systems may be free-standing, integrated into electronic health record systems or patient portals, or native functionality of an electronic health record. Despite potential benefits, there are challenges with integrating PROs into practice for monitoring patient status, as there are with any modifications to existing clinical processes. These challenges range from administrative to technical to workflow. A session at the 2018 ASCO Annual Meeting was dedicated to the implementation of PROs in clinical practice. The session focused on practical examples of PRO implementations, with honest reflections on barriers and strategies that may be generalizable to other systems looking to implement PROs. Panelists for that session are the authors of this paper, which describes their respective experiences implementing PROs in practice settings.

Patient-reported outcomes encompass data reported directly by people about how they feel and function, such as symptoms, physical function, and quality of life.

Although many PRO questionnaires were initially developed for use in clinical trials, there is rapidly growing interest to integrate PROs into routine clinical practice for monitoring patient clinical status. An impetus for this movement is the body of evidence demonstrating that clinicians miss about half of their patients’ symptoms during treatment.1,2 Downstream consequences of missing symptoms include patient suffering due to poor symptom control, missed treatments, emergency department visits and hospitalizations, and physical debility. Indeed, poorly controlled symptoms are a principal driver of preventable emergency department visits, such as for pain, dyspnea, dehydration, nausea or vomiting, diarrhea, and fatigue.3-4 Multiple studies show that systematic monitoring of patients’ symptoms using PROs closes this gap, improving patient-clinician communication, clinician awareness of symptoms, symptom management, patient satisfaction, quality of life, and overall survival.5-7

Despite the clear benefits, there are challenges with integrating PROs into practice for monitoring patient status, as there are with any modifications to existing clinical processes. These challenges range from administrative to technical to workflow issues. A session at the 2018 ASCO Annual Meeting was dedicated to the implementation of PROs in clinical practice. The session focused on practical examples of PRO implementations, with honest reflections on barriers and strategies that may be generalizable to other systems looking to implement PROs. Panelists for that session are the authors of this paper, and each has summarized his or her respective content in the below sections.

THE ERAPID SYSTEM IN ENGLAND

(GALINA VELIKOVA, MD, PHD)

The routine recording of treatment side effects experienced by patients with cancer is typically not well documented or easily accessible within medical records. Patients also report challenges understanding the clinical severity of particular symptoms and the appropriate care options when...
outside the hospital environment. In response to these issues, the eRAPID system was devised to allow online patient reporting during and beyond cancer treatment. Patients can remotely report symptoms and side effects from home and receive immediate severity-tailored advice on self-management strategies for mild symptoms or recommendations for contacting the hospital for serious problems. The system also generates notifications via email to the relevant clinical team for severe adverse events. Patient data are immediately transferred to electronic medical records (EMRs) for clinical staff members to access. These data can then be used in routine consultations to support clinician decision making and focus on symptoms that are most problematic for patients.

The overall aims of the eRAPID system are to improve the safe delivery of cancer treatments, enhance patient care, and standardize documentation of adverse events within the clinical data sets. We hypothesize that the eRAPID approach will bring benefits for both patients and health care professionals. For patients, it may enable earlier symptom detection and improved self-management, timely admissions to manage more serious toxicity, improved supportive medication use, and appropriate health service contacts. For staff members, it may reduce the number of contacts, save time spent on inquiring and recording adverse events, focus attention, and support decision making during consultations.

Some of these benefits have recently been shown in a randomized controlled trial of chemotherapy for metastatic cancers but also suggesting a survival advantage.7,8:

### TABLE 1. Severity-Based Clinical Algorithm, Patient Advice, and Frequency of Activation of Each Category in the Pilot Study

<table>
<thead>
<tr>
<th>Algorithm</th>
<th>Summary</th>
<th>Immediate Advice Message in QTool</th>
<th>Proportion in This Category in the Pilot Study (Total of 540 Completions), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>One or more severe problems likely medical emergency, experienced currently</td>
<td>You have indicated a serious problem in this area. We recommend that you contact the hospital now to discuss your symptoms with the medical team (St. James’s University Hospital tel. XXXXX and ask for the Oncology Patient Inquiries Bleep Holder).</td>
<td>2</td>
</tr>
<tr>
<td>A2</td>
<td>Severe problem(s) that improved</td>
<td>You have reported that you have been experiencing some serious problems which have now improved. If you have not already been in contact with your medical team, we recommend that you contact them to discuss your symptoms when convenient, or mention them at your next clinic appointment (if in the next 1–2 weeks). If you have already been in touch with your medical team regarding your symptoms, please follow the advice they have given you.</td>
<td>8</td>
</tr>
<tr>
<td>B</td>
<td>Three or more moderately severe medically important problems</td>
<td>If your symptoms are new or have changed recently, please either contact the hospital when convenient to discuss your symptoms with the medical team or mention them at your next clinic appointment (if in the next 1–2 weeks).</td>
<td>14</td>
</tr>
<tr>
<td>C</td>
<td>Mild symptoms, do not require medical attention at present</td>
<td>Follow self-management advice.</td>
<td>75</td>
</tr>
<tr>
<td>D</td>
<td>No problems reported</td>
<td>No advice. Thank you for completing eRAPID.</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

### PRACTICAL APPLICATIONS

- PROs reflect how patients feel and function and are measured via surveys.
- PROs can be collected via the internet, automated telephone systems, or downloadable applications.
- Multiple studies have tested whether it is feasible to integrate PROs into routine cancer care (it is) and whether outcomes are improved as a result (they are).
- Many institutions are integrating PROs into clinical practice and are identifying challenges and strategies for successful implementation.
- Like any quality improvement project, there is a risk for failure if implementation is not done thoughtfully with ongoing monitoring and adjustment, particularly in early phases, as described through practical examples in this paper.
FIGURE 1. Case Study of a Patient With Ovarian Cancer: Screenshots of the eRAPID Display in the Electronic Medical Record

(A) Graphic format particularly suitable for tracking changes over time (most recent report is on the right).

(B) Tabular format, contains free text on additional symptoms reported by the patient (most recent self-report is on the left).

Abbreviation: PRO, patient-reported outcome.
During the eRAPID development phase, we adopted the Medical Research Council’s complex intervention guidance to optimize the design and acceptability of the system. The intervention can be viewed as consisting of many active components, which must be individually developed and then put together and evaluated as a single complex system. The active components of eRAPID are described briefly below.

**IT System**

A robust, secure online system was developed that allows patients to log in with a provided user name and report their symptoms remotely; within a few minutes, the self-reported data are pulled behind the National Health Service firewall to a database linked to the EMR, where the patient is identified and his or her results are displayed as part of the individual medical record.9
Clinical Pathways
We performed process mapping of patient treatment pathways and interviews with health care professionals and patients to identify where and how eRAPID will best fit in the clinical flow and who are the key professionals to engage in the new approach.\textsuperscript{10}

Selection of Symptom Items for Patient Self-Reporting
We elected to use the Common Terminology Criteria for Adverse Events system, converting the adverse events items descriptors into patient self-reporting format preserving the severity grading. Cognitive patient interviews were performed to ensure comprehension and clinical meaningfulness of the items.\textsuperscript{11}

Severity thresholds and a clinical algorithm for severity-based patient advice and notifications were developed. The immediate severity-related guidance generated from eRAPID on how to self-manage mild symptoms and when to contact the hospital is a unique feature of our system compared with other electronic PRO Web portals. This feature was developed in an iterative process involving the oncology clinicians to determine the severity thresholds in a way that supports patient education, encourages self-management, but does not compromise patient safety. See Table 1 for details of the clinical algorithm’s categories, patient advice and frequency of activation.

Training of Patients and Professionals
The ultimate success of eRAPID is dependent on how patients and staff engage with and appreciate the potential benefits of the system. Patient training is provided initially face to face by a researcher who introduces the eRAPID system, gives patients their user names and passwords on a postcard, and shows a demonstration version of the questions, the automated advice, and the graphs of responses. Staff training consisted of a brief presentation at the initiation of the project, usually during existing team meetings to minimize time burden. Subsequently, during the routine outpatient clinics, staff members were shown again how to access patient self-reports and encouraged to discuss them and to record their actions to the notifications for severe symptoms. Recently, the staff training material was combined into an e-learning package, accessible via hyperlink directly from the patient records in the EMR.

Once the components were fully developed, we performed a usability field test of the live system in a clinical context. Twelve women receiving chemotherapy for early breast cancer used eRAPID for four cycles (approximately 12 weeks), and 10 clinicians were asked to use symptom reports during consultations and respond to notifications for severe symptoms. Feedback was positive. Patients described the system as “reassuring” and “comforting” and valued the self-management advice and the feedback on when is appropriate to contact the hospital. Some modifications were made to the clinical algorithm. For example, on a few occasions, patients reported severe symptoms retrospectively (the questions asked about the past 7 weeks), after they had been treated. Therefore, an additional branching question was introduced to verify that a severe symptom is current, thus avoiding unnecessary notifications.
eRAPID is currently undergoing an evaluation in a series of pilot and randomized controlled studies. A two-center pilot study in pelvic radiotherapy for prostate, gynecologic, and lower gastrointestinal cancers is looking at using eRAPID to monitor adverse effects during and up to 6 months after treatment.

A randomized controlled trial with an internal pilot is evaluating potential benefits for patients and the cost-effectiveness of the eRAPID intervention during chemotherapy for breast, ovarian, and colorectal cancers. The main outcome measures from the patient perspective include quality of life, self-efficacy, and costs to patients. From the health care perspective, data are collected on processes of care: clinical contacts with the hospital (acute admissions, telephone calls, ward stays, and unplanned appointments) and changes to chemotherapy delivery.

The internal pilot study suggested that the intervention was well received, and recruitment figures met the criteria for progression to the full trial. The pilot study recruited 87 participants over 6 months; 134 patients were identified, 25 were excluded after further screening because of lack of Internet access or language barriers, and 22 declined. The consent rate (excluding ineligible patients) was 80%. Thirteen participants withdrew (8 because chemotherapy was stopped). Five hundred forty online symptom reports were completed, and 11 severe symptom alerts to clinicians were activated. Information technology systems were stable, and participants reported very few problems accessing or using the eRAPID symptom reports. The full randomized controlled trial commenced in May 2016, and by the end of January 2018 had recruited 358 patients, aiming for a target sample of 417. Results will be available by the end of 2018.

Along with the formal assessment of the intervention in the randomized controlled trial, an ongoing experiential approach to observing and capturing the experiences of patient and professionals using the eRAPID system is being conducted. The main barrier for the professionals is the perceived extra time factor and the workload, despite previous research showing that patient encounters do not take longer. Lack of familiarity with the system is another major barrier. There is a learning curve when the self-reports are introduced, and the clinicians need to see a sufficient number to become comfortable using them. As this approach is tested in a randomized trial, only half of the patients have self-reports. One clinician will see only one or two patients per clinic and may forget to look at them. From the patient side, the main reason for noncompletion is when patients are admitted to the hospital because of toxicity or when they are doing well and are away from home.

Our observations suggest that a key facilitator for patients is the fact that their clinicians are using the self-reports during their care, and they can see the value of providing these data. Patients also valued the directions on when it may be appropriate to contact the hospital, as they did not want to burden the busy clinical staff. For clinicians, it is essential to find out for themselves that patient reports can provide useful data on symptom severity and track it over time and that giving a focus to the consultation may save time. Using patient reports to inform the management of patients’ conditions can be particularly powerful, as the following case study demonstrates.
Case Study
Figure 1 presents a case study of a patient with ovarian cancer, providing an example of how patient self-reports correspond to the clinical data and how they may add subjective information. The case is that of a 75-year-old woman diagnosed in 2011 with stage 3C/4 high-grade serous ovarian adenocarcinoma. No pathogenic gBRCA mutation was present. The patient was treated with chemotherapy with interval debulking surgery. Between 2012 and 2017, she received seven lines of systemic treatment, including bevacizumab, tamoxifen, carboplatin, paclitaxel, and liposomal doxorubicin. She participated in eRAPID from February to June 2017, when she had further recurrence with retroperitoneal lymph nodes, peritoneal and omental disease, and ascites. Presenting symptoms were abdominal pain and discomfort, nausea, poor appetite, fatigue, and limited daily activities. These symptoms were documented in the medical records and are well reflected in the self-reports (Fig. 1A).

Treatment with low-dose weekly paclitaxel and carboplatin for six cycles resulted in partial response on CT and normalizing of the tumor marker cancer antigen 125. Figure 1A shows corresponding improvements in abdominal pain, nausea, and appetite and less impact on daily activities. However, the patient progressively developed peripheral neuropathy, as can be seen from Fig. 1B, reporting pains in the fingers and toes. eRAPID reports showing an improvement of the recurrence symptoms confirmed the partial response on imaging and markers and later supported the clinical decision to stop the chemotherapy because of the development of peripheral neuropathy.

In conclusion, the eRAPID system is reliable and secure and is performing well during the ongoing studies. We plan to analyze and publish the results in 2018. If we confirm the hypothesized benefits for patients and professionals, as well as cost-effectiveness, the next step will be to move to wider implementation, on the basis of the science of diffusion of innovation and using change management methodology.

CANCER CARE ONTARIO PRO PROGRAM (LISA BARBERA, MD)
Cancer Care Ontario (CCO) is the provincial government’s adviser on the cancer system and is accountable to the Ontario Ministry of Health and Long Term Care. CCO leads multiyear system planning, contracts for services with hospitals and providers, deploys information systems, establishes guidelines and standards, and tracks performance targets. The province of Ontario has a population of approximately 14 million people and covers a geographic area similar to France and Spain combined. The province is divided into 14 regions, each assigned to a regional cancer program.
Regional cancer programs are responsible for service delivery but also for implementation of provincial programs.

All programs and activities at CCO are aligned with the Ontario Cancer Plan. In 2015, Ontario Cancer Plan IV specifically identified the importance of PROs. Although CCO has been collecting PROs since 2007, this explicit strategic objective provided clear guidance regarding the importance of PROs for the organization and the creation of a formal PRO program in 2013.

The origin of the PRO program lies within the provincial Palliative Care Program, which was formed in the mid-2000s. Within that context, symptom management was identified as a real gap in clinical care. A pilot project was completed at a single regional cancer center to evaluate the role of routine administration of the Edmonton Symptom Assessment Scale (ESAS) within clinical care. The pilot project demonstrated increased documentation of symptoms and decreased acute care use. CCO implemented ESAS provincially at all regional cancer centers in 2007. Initially, only palliative care clinics and lung cancer clinics were included. In the ensuing years, the scope broadened to include all patients with cancer, regardless of cancer type or disease status. Since that time, ESAS has been a part of routine cancer care for all patients attending any of the 14 regional cancer centers. Implementation has continued to expand to include many of the partner community hospital sites and has been integrated into many of the local EMRs. Across Ontario, approximately 30,000 to 40,000 unique patients respond to ESAS on a monthly basis.

Although local implementation looks different at different centers, a typical workflow includes a three-step process: (1) the patient registers for the appointment at the front desk, (2) the patient is directed to the computer kiosk to complete the PRO questionnaire electronically (Figs. 2A and 2B), and (3) PRO scores are provided to the clinical team (Fig. 2C). Patients arrive and register for their appointments. They are directed to a kiosk in the waiting room or perhaps given a tablet. They answer the nine symptom questions from ESAS and one question about functional status using a touch screen interface. A hard copy of the output includes a histogram with symptom scores for the past 20 visits. Some centers have this available in their EMRs. The output is then given to the clinical team to use within the encounter. CCO has developed both provider-facing and patient-facing symptom management guides for each symptom found in ESAS. These are intended as guidance for the clinical care team on how to respond to elevated symptom scores (www.cancercareontario.ca/en/symptom-management).

With more than a decade of experience with ESAS, CCO decided to offer disease-specific measures. ESAS covers symptoms common to all patients with cancer. Indeed, it covers 7 of the 12 symptoms identified by the National Cancer Institute as core symptoms for inclusion in clinical trials when a PRO is being measured. However, certain subgroups of patients have particular symptom issues not covered by ESAS. For example, men with early-stage prostate cancer have urinary difficulties, bowel symptoms, and sexual health issues. A pilot study of the Expanded Prostate Cancer Index (EPIC-26) at one cancer center demonstrated positive feedback from both patients and providers. On the basis of the initial pilot work, a follow-up study was conducted with a total of four cancer centers, this time with EPIC-CP (Clinical Practice). Quantitative and qualitative data from patients and providers were overwhelmingly positive. Using EPIC-CP fostered patient-centered communication; patients felt better able to communicate their experience to the team, it improved communication and shared decision making, and facilitated multidisciplinary team care. The need for education and support for patients and providers emerged as an important implementation issue (manuscript submitted).

FIGURE 6. Example Workflow for Integration of PRO Information Into Clinical Practice From the UNC/ALLIANCE/PCORI PRO-TECT Trial

Abbreviations: PRO, patient-reported outcome; PCORI, Patient-Centered Outcomes Research Institute; UNC, University of North Carolina.
FIGURE 7. Screenshots From the UNC PRO-Core System

A  Smartphone patient interface from UNC PRO-Core system

B  Clinician longitudinal report from UNC PRO-Core system

UNC, University of North Carolina; PRO, patient-reported outcome; ECOG, Eastern Cooperative Oncology Group.

(A) Smartphone patient interface from the University of North Carolina (UNC) PRO-Core system. (B) Clinician longitudinal report from the UNC PRO-Core system.
On the basis of this evidence and experience, CCO decided to implement EPIC-CP provincially starting in October 2016. An additional item about rectal bleeding (taken directly from EPIC-26) was added to the existing EPIC-CP questions to ensure that this important radiation side effect was explicitly captured. Twenty-one support resources were developed with input from 95 stakeholders representing a wide variety of backgrounds such as physicians, nurses, dieticians, psychologists, information technology experts, and patients.

These materials included patient- and provider-facing symptom management guides for each EPIC domain, training videos about how to interpret the scores, technical documents for Health Level 7 integration, slide shows for volunteers (who often help at the kiosks), and frequently asked question sheets. CCO staff members were better able to support local implementation efforts by virtue of a staggered or waved rollout (a few centers at a time). CCO staff members visited each site prior to the go-live date and reviewed a detailed project implementation plan outlining the required steps over the ensuing 4 to 6 weeks. CCO staff members also provided change management ideas, materials, and support for IT integration and help with stakeholder engagement. By January 2017, successful launch had occurred at 12 of the 14 regional cancer centers, with more than 10,000 assessments captured to date. During the implementation phase, CCO staff members facilitated a community of practice that was attended by frontline individuals from the regional centers. This provided a safe space for problem solving and learning from peers doing similar work at other sites.

The intention is to eventually have cancer-specific measures for the common cancers and/or those with a particularly heavy symptom burden (e.g., head and neck cancers). As such, there is a need to standardize the approach to this process. A PRO advisory committee was created with individuals with methods expertise and regional and patient representation. A pipeline approach to select and implement PROs was drafted with specific steps and considerations along the way (Fig. 2). A disease site is selected on the basis of disease burden, symptom burden, and any windows of opportunity that would ease implementation. A review of the literature identifies candidate measures. Measure choice is made on symptom coverage, usability (e.g., the number of questions), and its psychometric properties. A pilot study evaluates the acceptability of the measure, its impact on outcomes, and sustainability issues. A decision regarding implementation is made on the basis of these considerations. Provincial implementation would involve the development of support materials and a waved implementation approach. A formal evaluation is completed to inform subsequent implementations. The intent is for the PROs advisory committee to have oversight of this process and to work in close partnership with the relevant provincial tumor sites.

CCO holds quality of care as a key value and performance management is an important organizational role. On a quarterly basis, each regional cancer program is issued a report on a range of indicators that span the cancer continuum. The proportion of eligible patients assessed with a PRO measure is included in this report. Annual reports of the same measure are included on the Cancer System Quality Index (www.csqi.on.ca), which is publicly accessible. Although assessing symptoms is one component of care, symptom management is also critical. An annual ESAS experience survey is administered to a convenience sample of patients and asks questions about their satisfaction with symptom management. This is also reported on the Cancer System Quality Index. An annual chart audit of a sample of charts from patients with high symptom scores evaluates whether the elevated symptom score was acknowledged, further assessed, and intervened upon. The chart audit results are provided back to local teams for local quality improvement initiatives.

There are several factors that have facilitated implementation efforts. These include broad-based stakeholder involvement in as many steps as possible, EMR integration, central support of local change management, and identifying a local clinical champion. Combining patient- and provider-facing symptom management guides together with the PRO measure when implementing has also proved important.

**BUILDING AN ORGANIZATION-WIDE PRO PROGRAM AT DARTMOUTH-HITCHCOCK**

(CAROLYN L. KERRIGAN, MD, MHCDS)

Dartmouth-Hitchcock Medical Center (DH) in Lebanon, New Hampshire, is licensed for 400 beds and is the state’s only academic medical center. It is also the state’s only tertiary referral center, National Cancer Institute-designated comprehensive cancer center, level 1 trauma center, and comprehensive full-service children’s hospital. DH extends its reach in New Hampshire and Vermont via 4 ambulatory facilities, 11 regional clinics, and 22 outreach clinics.

In addition, DH has affiliations with four community hospitals in Vermont and New Hampshire. DH has long been interested in measuring outcomes that matter to patients. In 1997 DH opened the Spine Center, with electronic integration of PROs to support clinical care and research. Since then, there has been continued leadership support to expand this program throughout the hospital and system. This has involved partnering with four different technology vendors as the program has been scaled up. In 2011 DH migrated from a home-grown electronic health record (EHR) to EPIC’s EHR, and DH has since leveraged its relationship with the vendor to push for enhanced features within their software to help meet DH’s goals of collection, use, and learning from PROs.

The first phase of our work focused largely on growing the technology infrastructure in two ways: (1) delivering questionnaires to patients electronically (through a patient portal, on smart phones, or on a tablet in clinic) and (2) to provide immediate access to results by the care team. Our early adopters needed minimal training and minimal
instruction in the use of PROs, as they were highly engaged and recognized the value of PROs. As we began scaling up the program and building PRO questionnaires for an ever-expanding number of clinical areas, it became evident that we needed a more robust approach to understanding roles within the clinical teams, workflows, assisting with redesign for each clinic, and education of score interpretation and potential interventions.

We currently have deployed questionnaires that include a mix of individual items (demographics, symptom presence, function, etc.), and questionnaires that are scored (PRO measures) for more than 40 different health conditions. This amounts to 4,500 individual items, 440 scoring questionnaires that have been assembled into more than 100 questionnaire sets for use by different clinical areas. This number is continually growing. In the last 12 months, our system has supported the ordering of more than 130,000 questionnaires, with a response rate averaging 79% and some clinics seeing response rates in the 95% range. Figure 3 includes a sampling of questionnaires containing PROs that can be ordered by care team members throughout the system.

With this robust infrastructure in place, we have defined 12 steps in PRO implementation. Steps 1 to 6 are considered basic and steps 7 to 12 advanced.

Step 1: Implementation begins with an inquiry from a clinical area (bottom up) or a strategic initiative (top down) that could benefit from PRO implementation. In the early years of our program, the majority of new PRO implementations began with inquiries from clinical areas (e.g., the Spine Center), our early adopters. More recently there have been strategic initiatives aligned with new care models that have led to PRO implementations (e.g., systematic screening and outcome tracking for depression).

Step 2: A formal application is submitted. This application was designed by our steering committee so that it could collect standardized information from requestors, understand the size of the population that would be responding to PROs, and determine the number of clinicians involved. This allows the committee to set priorities for programming and training resources when the demand exceeds our capacity.

Step 3: A formal consultation with the requestor and steering committee members is undertaken to identify patient design opportunities, advise on selecting validated PROs, avoiding redundancy in the health system (e.g., choosing one standardized PRO to screen for depression), exploring composition and roles of the local care team and the implications of workflow changes. During this initial consultation, we also begin to educate the team on EHR functionality: finding and using results with patients and learning how to document efficiently.

Step 4: The new PRO questionnaire is built into the EHR for both collection and scoring. This also involves formatting display of results and developing basic documentation tools. Figure 4 provides a sample of two such documentation tools.

Step 5: The PRO is piloted with one provider and one patient with at-the-elbow support. The PRO is manually assigned to the clinic visit using tools within EPIC. The experiences at this initial visit help troubleshoot any issues, provide just-in-time education, and make adjustments as needed using principles of agile design. Care teams are also instructed in how to send patients PROs attached to a secure message so that questionnaires can be completed between visits as needed.

Step 6: The use of PROs is expanded to additional providers and to all patients who meet criteria for completing a PRO. This is accompanied by care team education on where to find results, tools for documentation, and the interpretation of scores. Step 6 also ensures that the care team members share the results with patients and integrate a discussion of the PRO scores just as they would any other laboratory or imaging result. At this stage of maturation, we also begin to share with care teams a dashboard of process measures such as trends in questionnaire completion rates and location (patient portal vs. clinic) where PROs were completed.

Step 7: More advanced steps then follow, most commonly but not always in a linear order. The seventh step is to use discrete elements in the medical record, such as type of clinic, provider, gender, age, history of prior PRO completion, and diagnosis, to automatically queue the PRO for an upcoming clinic encounter rather than requiring a manual process to “order” a questionnaire. We also program rules as to how far in advance of an encounter the PRO is released for the patient to complete, as some patients prefer to complete their PROs via our patient portal or personal device in advance of the visit rather than on a tablet at the time of the visit. Programming logic can also be used to suppress PRO questionnaires on the basis of time since prior completion. If two clinical areas are interested in the same PRO, this avoids the burden for patients of recompleting a PRO that they have just completed recently for another clinic.

Step 8: A closer look is taken at roles in the clinic and determines who on the team should be looking at results and how they should be used by whom. Examples are as follows: (1) in a clinic with an embedded behavioral health clinician, the care team may have determined that it is the role of the behavioral health clinician to respond to a positive depression screen rather than the primary care provider; (2) in a clinic with embedded physical therapists, the care team may have decided that both specialist and
therapist should track and discuss results with patients; (3) in yet another clinic using PROs to screen for social determinants of health, the role of managing results may fall to a community health care worker; and (4) in an oncology clinic, a nurse may be best positioned to review results with patients.

Step 9: Often the results of PROs are new to the care team, and they are unfamiliar with their interpretation and the response warranted. Building decision support tools into the EHR can provide needed guidance to manage abnormal results. Figure 5 shows one such tool. Also, building data displays that include traditional clinical measures alongside PROs can provide meaningful insights.

Step 10: Care teams may discover that they need new resources to manage abnormal results. This leads to careful consideration of the current workforce, tasks assigned, and determination of whether some tasks can be eliminated and others reassigned or if new team members with unique skill sets are needed.

Step 11: Once PROs have been collected for some period of time, it is important to plan for population-level analytics. The results from these analyses can provide important process and outcome measures to the care team and to leadership. They can help build the case for new resources and help recognize gaps in care. The results can be fed forward to clinical teams to help predict outcomes for subsequent patients with similar characteristics. Our spine program has reached this level of maturity (http://calgary.dartmouth.edu/SpinalOutcomes/).

Step 12: Using the power of the data to provide performance feedback to departments, frontline care teams and in some cases individual providers after appropriate risk adjustment. We have reached this level of maturation to date with two of our programs: depression management in primary care and total joint replacement.

Barriers we have encountered include the following: (1) If the steps are taken too quickly (e.g., patients complete the PROs, but no one on the care team discusses the results with patients, and in fact care team members ask many of the same questions conversationally), patients are left wondering why they bothered. Patients can become disengaged and decline to participate further in PRO collection. (2) Enhancements to the EHR such as a patient-friendly dashboard of results can take many years to achieve. (3) For small clinical programs, it may be difficult to easily make sense of the population-level analytics. For these small programs, data sharing with other organizations can be complicated by technical challenges and lack of standardization of which PROs to use. (4) If one organization has built a PRO questionnaire into its EMR, it is often not possible or easy to make this same PRO available in another organization’s EMR without completely rebuilding it, even when using the same vendor. (5) Because of this, some of our clinical programs that are participating in learning collaboratives have chosen to use a PRO collection system endorsed by the collaborative but outside our EMR. This can create barriers to full use of PROs at the point of care and integration of the data with the local EMR.

DH’s future vision is to have an enriched information environment that will be used to support patient decision making using principles of coproduction of care plans. This will require an IT platform that supports full integration in a local EMR and seamless sharing of deidentified data with collaborative networks. These data should include not only PROs but other relevant clinical data such as defined by groups such as the International Consortium for Health Outcomes Measurement (www.ichom.org). The collaboratives can then learn, through analysis of large data sets, how different patient characteristics and different treatment interventions affect patient outcomes on a scale that cannot be achieved by one individual organization, resulting in improved outcomes.

**PRO IMPLEMENTATION RESEARCH AT MEMORIAL SLOAN KETTERING CANCER CENTER AND THE UNIVERSITY OF NORTH CAROLINA (ETHAN BASCH, MD, MSC)**

Several large studies of PRO implementation in routine cancer care contexts have been spearheaded by a team initially located at Memorial Sloan Kettering Cancer Center and subsequently at the University of North Carolina. These studies have focused on identifying approaches to implementation and effectiveness that are successful across populations.

The general PRO approach has included a brief electronic symptom survey including 10 to 15 questions derived from the patient version of the National Cancer Institute’s Common Terminology Criteria for Adverse Events, administered via Web or an automated telephone system (patient choice), with alerts to nurses for severe or worsening symptoms. Patients have generally been asked to self-report on a weekly basis, with reminders sent by email, text, or automated phone message (Fig. 6). More recently, symptom management pathways for patients and clinicians have been triggered by these alerts.

This has included the Symptom Tracking and Reporting system, the use of which was associated with significantly improved quality of life, physical functioning, longer tolerability of chemotherapy, reduced emergency department visits, and lengthened overall survival in a large single-center randomized trial at Memorial Sloan Kettering Cancer Center. This system, and its outgrowth through the PROCore at the University of North Carolina (Fig. 7), are being used in multiple national assessments of PRO integration into clinical care, including the ongoing Patient Centered Outcomes Research Institute—supported PRO-TECT trial (NCT03249090). PRO-TECT is a U.S. national cluster randomized trial in 1,000 patients treated at community oncology practices, in which practices are assigned to integration of electronic PROs or usual care. Both arms are provided with standardized symptom management pathways for patients and providers. Outcomes include measures of utilization...
and clinical outcomes, as well as assessment of implementation challenges and successes. A goal is to inform ongoing efforts to implement PROs in oncology practice.

**CONCLUSION**

The PRO implementation experiences described in this piece demonstrate the progress of a nascent field that has moved from research and theory to application in practice. These examples show that it is feasible to implement PROs in clinical practice. However, as with any quality improvement project, there is a risk for failure if implementation is not done thoughtfully with ongoing monitoring and adjustment, particularly in early phases. The examples herein provide insights about potential pitfalls and strategies when considering implementation.

A more in-depth description of the various considerations for bringing PROs into a practice can be found in two excellent users’ guides, which are freely available online and are highly recommended: the User’s Guide to Implementing Patient-Reported Outcomes Assessment in Clinical Practice from the International Society for Quality of Life Research and the Users’ Guide to Integrating Patient-Reported Outcomes in Electronic Health Records supported by the Patient-Centered Outcomes Research Institute.

Moving forward, it is our hope that PRO implementation efforts will learn from these collective experiences to thoughtfully design and roll out programs—with adequate resources, training, and continuous monitoring—to optimize the likelihood of success.

**References**


Understanding Utilization Management Policy: How to Manage This Increasingly Complex Environment in Collaboration and With Better Data

Debra A. Patt, MD, MPH, MBA

Overview

As innovation in cancer care continues and newer costly therapies receive approval, utilization management will continue to grow as an important way that payers can attempt to control costs and value while providing service to their patients. Although utilization management may be necessary, it takes many forms and is optimized when it ensures appropriate patient access to services and minimizes administrative burdens of physicians and staff. These opportunities are best explored in collaboration with payers. Information systems today provide an excellent platform for data sharing to facilitate collaborative efforts between care delivery organizations and payers to optimize these efforts. As state and national policies differ regarding utilization management, it is important for clinicians to be both aware and involved.

Utilization management policy has many forms, but has become increasingly complex as cancer scientific discovery has blossomed, cancer subtypes have become more numerous, therapeutic opportunities have grown and become more specific, and clinical decision-making is infused with a complex integration of the patient, the disease, the state, and frequently molecular phenotypes. Utilization management was set forth with the goal of restricting use to that which is most appropriate and preserving quality and value.

Utilization Management Is Necessary To Control Costs and Quality

Although utilization management has become an increasing administrative burden and is a barrier to patient satisfaction in addition to an economic and efficiency hazard in many practices, it is also a necessary practice to appropriately control costs, curtail non–evidence-based therapeutic enthusiasm, and serve as a quality control to make sure the right patient is getting the right treatment at the right time. Content knowledge among medical oncologists is variable. Many states do not require maintenance of certification, and oncologists who have been practicing for more than 17 years are not required to recertify and demonstrate proficiency in oncologic knowledge, even in states that require maintenance of certification. From ASCO’s oncology census, we know that more than 18% of practicing oncologists are over age 64.¹ This means many oncologists have not taken a medical oncologist board examination since 1990, when the American Board of Internal Medicine grandfathered participation in oncology certification examinations.² Although certification does not imply proficiency, nor does lack of certification determine lack of proficiency, oncology is rapidly changing. Since that time when maintenance of certification was required, more than half of cancer drugs have been newly approved. In that same time period, cancer treatment costs have increased. In the last decade, there has been unprecedented scientific progress in cancer partnered with an exponential increase drug approvals for cancer drugs by the U.S. Food and Drug Administration (FDA; Fig 1).

This Has Been Partnered With Substantial Increases in Costs

It is useful to consider how we move forward in collaboration with better data from what we have learned, as the best answers for patients, practitioners, and payers lie in patients having access to the most effective therapies and achieving cure and disease control in an effective and efficient way so as to detour or defer subsequent health care costs and improve quality of life.⁴

ASCO published a comprehensive statement on utilization management for cancer therapy in April 2017.⁵ That statement focused on having appropriate access to cancer therapies for patients and charted better ways to move forward.

Utilization management in oncology comes in many forms and has many targets. Formulary restrictions, step therapy,
prior authorization, and peer review are the common types of utilization management typically integrated into coverage determinations. Diagnostic and therapeutic targets for utilization management are usually focused on some of the most costly interventions in cancer care: chemotherapy, including targeted therapy and immunotherapy, imaging, molecular testing, radiation therapy, surgery, and hospitalizations. Further discussion will be limited to consideration of medical therapeutic interventions in treatment with drugs, as this has been a growing challenge for patients and clinicians and represents a great opportunity for collaborative solutions that can be applied to the other targets as well, though the discussion is applicable to many of the medical diagnostic and therapeutic interventions, and they pose similar challenges and opportunities.

Practically, as an oncologist, utilization management has grown to dramatically affect patient care. In the last decade of practice, prior approval for chemotherapy treatment has gone from 48 hours to more than a week, and even longer for some therapies. The administrative burden, clinical inefficiencies, treatment delays, and patient satisfaction with delays in the prior authorization process poses problems on many fronts. Particular utilization management techniques in specialty pharmacy utilization should have consideration for improved collaboration and efficiencies. Although practitioners often are dissatisfied with the administrative burdens posed by utilization management strategies, they are an important quality- and cost-control mechanism that is ripe for collaborative solutions.

RESTRICTIVE FORMULARIES

Restrictive formularies are often a mechanism of utilization management used by health systems. Formularies will frequently view drugs within a certain class or within a given indication as therapeutically interchangeable. Although therapeutic substitution may be reasonable for some diseases and some treatments, therapeutic equivalency may not be established in cancer care. There also may be subtle indications why patients may be better candidates for one treatment versus another treatment similar in efficacy based on toxicity. A good example of this is in CDK4/6 inhibition in patients with estrogen-sensitive metastatic breast cancer. Although we have no comparative data to suggest efficacy is different among palbociclib, ribociclib, and abemaciclib, toxicity may make one choice better than another. For example, if a patient is intolerant of endocrine therapy...
due to toxicity, abemaciclib has single-agent FDA approval, whereas the other two agents do not. Similarly, if chronic diarrhea is a problem not amenable to medical management, palbociclib or ribociclib might be more optimal choices. For these reasons, restrictive formularies in cancer therapeutic interventions pose hazards for doctors and patients in getting the right intervention to the right patient at the right time. There may still be reasons why formulary management is preferable for a payer. In many state Medicaid programs in which the budget is truly limited, this blunt instrument may be the only feasible way a state program with limited staffing and limited budget can provide some treatments. Although in cancer care this treatment strategy is suboptimal, if it is implemented, inclusion of clearly articulated exception processes that have appropriate clinical oversight to enhance the therapeutic appropriateness of treatment decisions for patients receiving care is critical. The natural consequence of these formulary restrictions is often a worse outcome for patients, and whereas savings in decreased drug utilization are common, they are frequently offset by increased downstream costs of increased utilization due to worse outcomes.6

Incremental therapeutic strategies like step therapy, fail first therapy, and tiered therapy are inherently problematic in cancer care. Step or fail first therapies require a patient fail a lower cost therapy before being approved for a higher cost therapy. Although this may be a reasonable way to approach some medical problems for which the consequence of failing first is neither psychologically traumatizing nor life threatening, in cancer care, this is not an appropriate management strategy. Similarly, tiered therapy strategies with higher out-of-pocket patient costs for more expensive and more effective drugs impose a tremendous financial burden on patients that is suboptimal.

PRIOR AUTHORIZATION

Prior authorization is one of the most common types of utilization management we see in oncology. Frequently, payers or an external vendor hired by payers seek to gain information from the medical treatment team to determine if the proposed therapeutic intervention is appropriate. Prior authorization management varies in the degree of sophistication of the clinical reviewer. The data required to inform treatment decisions and oncology care are numerous to populate the decision tree along the line of therapeutic intervention. Sometimes prior authorization reviewers have specific oncologic knowledge, but many have not been in practice for some time over a time of remarkable innovation and change in cancer care. Sometimes prior authorization reviewers have very limited oncology experience and are simply following a treatment algorithm given to them. If patients fail to get approval for therapy through the prior authorization process, peer-to-peer reviews are frequently implemented. The peer-to-peer review process is important, but many peer reviewers have limited oncology experience or have not practiced since an era when half of the numbers of drugs were available.

PATHWAYS: A BETTER OPTION

Although all of these processes have their place, pathways programs that provide the critical data elements that guide clinical decision-making are a better option to control cost and quality. A more optimal approach is participation in evidence- and value-based treatment pathways that facilitate evidence- and value-based systems to improve patient outcomes and reduce the total cost of care.7,8 By facilitating evidence- and value-based choices, the goals of utilization management are satisfied while reducing the administrative burden in practices and allowing doctors to make point-of-care decisions for their patients without unnecessary treatment delays and changes seen in the prior authorization process. Pathways systems can be complex, and ASCO’s policy statement provides useful benchmarks to proceeding with a high-quality pathways system.9 Although pathways systems aim to provide the right treatment for the right patient at the right time, some practices struggle with managing many different pathways vendors in their own clinics. The administrative burden of the lack of parsimony in utilization management strategies is high and diminishes time clinicians can devote to patient care.

MOVING TOWARD VALUE-BASED CARE

As we move along the continuum to value-based care, value-based pathways are an important quality and value metric by which payers can manage utilization and preserve patient-focused care.10 These strategies have been useful in increasing compliance with evidence-based care and improving the value of care delivery. They have been incorporated into alternative payment models successfully and are an important part of quality and value in the Oncology Care Model and in the structure of other alternative payment model contracts.11 As all of our practices have growing engagement with value-based care, pathways establish a process by which patients, providers, and payers can be aligned toward common goals.

With better electronic health records and data systems, information from these pathways can be directly fed to payers to provide appropriate clinical data and reduce the administrative burden and inefficiency in the prior authorization process today. This is a more effective tool to get the right treatment to the right patient and can be electronically communicated to payers as our information systems continue to improve.

Clinical decision support can be used at the point of care to facilitate evidence-based decisions, ease the administrative burden of providers in completing this necessary documentation, and improve compliance with evidence-based treatment decisions and assessable data between clinicians and payers.12

As we practice on an individual level to provide the right care for each patient, our systems that support us in care delivery can assist in the provision of aligned action toward evidence- and value-based treatment choices to enhance the quality of care by facilitating evidence- and value-based
choices and using collaborative information systems to track and report to reduce the administrative burden and lack of efficiency seen in practice today. Payers and practices who are early adopters of these collaborative strategies will be farther down the path of systematically providing high-quality and value-based care.

References


Assessing the Value of Next-Generation Sequencing Tests in a Dynamic Environment

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OVERVIEW
Next-generation sequencing (NGS)–based technology has lowered the cost of cancer testing for genomic alterations and is now commercially available from a growing number of diagnostic laboratories. However, laboratories vary in the methodologies underlying their tests, the types and numbers of genomic alterations covered by the test, and the clinical annotation of the sequencing findings. Determining the value of NGS tests is dependent on whether it is used to support clinical trials or as a part of routine clinical care at a time when both the investigational drug pipeline and the list of U.S. Food and Drug Administration–approved or Compendium-listed therapeutics is in a high state of flux. Reimbursement policy for NGS testing by the Centers for Medicare & Medicaid is evolving as the value of NGS testing becomes more clearly defined for specific clinical situations. Patient care and clinical decisions-making are dependent on the oncologist’s knowledge of when NGS testing has value. Here, we review principles and practice for NGS testing in this dynamic confluence of technology, cancer biology, and health care policy.

NGS-based testing is a technology in evolution—evolving from completion of the human genome mapping in 2003, which at that time, relied on laborious older technologies, some of which, such as Sanger sequencing, remain the gold standard for DNA analysis. Instead of sequencing being performed one nucleotide at a time, genomic material is fragmented into shorter lengths of approximately 100 base pairs. These shorter fragments are sequenced in parallel, and much as a jigsaw puzzle is reconstructed by referring to a complete image, the short genomic sequences are mapped to one or more reference human genomes.1 The precision of this massively parallel sequence mapping is highly dependent on technical factors, such as the number of times that a nucleotide is repetitively sequenced (depth of coverage) and the computational algorithms used to map the nucleotide position. The pace of technologic evolution in genomics continues to accelerate, reducing cost and test turnaround time of NGS tests, while simultaneously increasing cost through the introduction of new technology, wider adoption of that technology, which may be premature, and downstream consequences on medical decision-making. The ultimate value of any diagnostic test is its impact or lack thereof on the clinical treatment of patients, which is dependent on knowing when to obtain the test in question and whether therapeutic choices exist that can be exploited. Just as genomic testing technology is in a continuous state of evolution, the pipeline of new therapeutics targeted to an expanding knowledge base of genomic and immunologic drivers of malignant behavior is increasing in parallel. The cancers of individual patients are also in a dynamic state, with clonal evolution and acquired resistance refuting a one-cancer, one-driver mutation model. These considerations illustrate the interdependency of factors that are relevant to assessing the value of NGS and other future genomic-based tests of the genome, transcriptome, proteome, and metabolome of individual patients with cancer. Ultimately, assessment of overall utility necessitates an understanding of the technical performance limitations of the test, the role of these tests in clinical trials enterprise design, and the use of these tests in routine patient treatment.

INTRODUCTION
Technical Performance
The first molecular-based cancer tests focused on a single protein or gene of interest, with great focus on standardizing the test methodology and defining cutoff points for determining the division of patients into categories of differing prognostic outcomes or differing predicted responses to therapy, such estrogen and progesterone receptor measurement in breast cancer and HER2 testing in gastroesophageal adenocarcinoma cancers.2,3 For particular anatomically defined cancers, grouping of molecular tests has become standard practice: estrogen and progesterone
receptor and HER2 for breast cancer and EGFR, ALK, and ROS-1 for adenocarcinoma of the lung. The U.S. Food and Drug Administration (FDA) policy describes companion diagnostic tests, which are developed in conjunction with new molecularly targeted agents.\(^4\) However, NGS panels comprise hundreds of genes and shift the quality testing assessment away from individual test performance to the performance of the underlying testing platform. Commercially available NGS varies considerably from laboratory to laboratory with regard to multiple factors, such as number of genes tested; whether limited hot spots, whole exons, or adjacent introns are being tested; and the technology of the underlying platform. Genomic alterations include single-nucleotide variants, copy number changes (amplification), and structural abnormalities ( insertions/deletions, inversions, and translocations), and the performance of different testing platforms varies by the type of genomic alteration being studied.\(^1\) Discordant sequencing reports among commercially available NGS have been reported.\(^5,6\) Balancing the need for widely accepted and adopted standards for genomic test development and performance while retaining the flexibility and agility needed for rapid innovation is the first challenge to improving the value of NGS. An excellent review of the underlying issues pertinent to biomarker-based test development in oncology was published in 2015 by De Gramont et al.,\(^7\) although without a specific focus on NGS. The same month, the College of American Pathologists (CAP) published the CAP Laboratory Standards for Next-Generation Sequencing Clinical Tests with 18 new laboratory accreditation checklist requirements that were incorporated into the CAP molecular pathology checklist.\(^8\) Together, these two publications describe fundamental, consensus-driven principles by which an NGS testing laboratory can be measured against.

The CAP standards separate NGS into wet and dry laboratory components, which is useful, because each has a clearly distinct delineation and in fact, could be performed by two separate laboratories working together as pragmatic considerations may dictate. For example, an entity might decide to limit its investment to one or the other depending on access to capital and intrinsic expertise. Wet laboratory processes encompass specimen handling, genomic material extraction and preparation, mapping of massively parallel short reads to the reference genome, and subsequent reporting of the genomic sequence as FASTQ files with annotation describing the precision at each nucleotide location (base quality score) or target region. Emphasis is placed on specifying standard operating procedures, documentation of testing procedures, and quality assurance programs.

Dry laboratory refers to the bioinformatics component of NGS. Starting with the generation of the FASTQ file describing the reconstructed sequence reads, analysis is performed to identify variants from the reference genome that may be reported as condensed binary alignment map or BAM files, because data storage and transmission are a rate-limiting consideration as the number of genes studied increases. Genomic variants are then cross-referenced to one or more digitally accessible knowledge bases that provide information on the possible causative relationship and therapeutic impact of that genomic variant on patient disease state. A genomic pathology report is then generated with clinical annotation.

**Clinical Trials Enterprise**

NGS tests differ from single-analyte tests by the number of the genomic targets being studied within a panel, most of which lack an inherently obvious biologic connection to the patient’s cancer. Association versus causation becomes an issue of concern when interpreting the relevance of the genomic finding to a patient. NGS testing generates a great number of observations per sample tested, and such high-dimensional data are susceptible to overfitting of the data by computational models. Yet, increasing reliance on computational modeling and “black box” algorithms seems inevitable after we accept that the one-gene, one-disease model does not apply well to most cancers or most patients, because their individual cancers undergo clonal evolution and selection over time. The National Academy of Medicine defines an omics-based test as “a complex form of a biomarker test, using a defined set of measurements combined with a computational model as a clinical test.”\(^9\)

Premature adoption of technology has undisputable risk to patients and society. The widespread adoption of high-dose chemotherapy with hematopoietic stem cell support in breast cancer was a lesson that should not be necessary to relearn. Yet, we have already witnessed this with respect to predictive biomarker use in a series of clinical trials designed around a critically flawed omics-based test developed at Duke University.\(^5,10\) The National Academy of Medicine’s *Evolution of Translational Omics: Lessons Learned and the Path Forward*\(^9\) sought to draw on this experience and articulate principles and processes to guide development of omics-based tests in oncology. The charge to the National Academy of Medicine committee was specific to the use of omics-based tests in the context of clinical trial design and was not for the definition of clinical utility: “the

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## PRACTICAL APPLICATIONS

- NGS testing is a more efficient and timely technology for genomic profiling of cancer, because it minimizes the amount of tissue consumed and avoids the need for iterative reflex testing.
- The selection of a diagnostic testing laboratory may impact the clinical utility of the NGS testing result.
- Greater use of NGS testing will allow the discovery of rarer driver mutations.
- Improper or premature adoption of NGS testing may negatively impact patient outcomes if there is an insufficient evidence base underlying decision-making.
- Molecular tumor boards allow molecular pathologists and clinicians to integrate NGS genomic reports in the context of a broader knowledge base and the individual patient to support better treatment decisions.
processes and criteria for adoption and use of omics-based test in standard clinical practice are outside the scope of this report.19 The committee separated its report into two phases. The first, test discovery and validation, overlaps with the subsequent CAP report. The second phase, evaluation of clinical utility and use in a clinical trial context, describes three study designs based on successful and ongoing trials. The emphasis on clinical trial design limits the focus to drug development for FDA evaluation, and FDA evaluation does not include assessment of clinical utility or benefit coverage policy. Nevertheless, the evidentiary base created in the context of clinical trial use of omics-based tests can be directly relevant to establishing a clinical, reimbursable standard of care.

The current use of NGS testing in clinical trial design is most useful for biomarker-driven selection of patients for clinical trials. The argument for large panel testing of genes is that patients with less common mutations associated with specific anatomically defined cancers can be identified and placed in relevant studies or identified for trials using biomarker-driven basket-bucket design, such as the National Cancer Institute’s Molecular Analysis for Therapy Choice (MATCH) and ASCO’s Targeted Agent and Profiling Utilization Registry (TAPUR). Underlying this premise is that biomarker-driven studies produce superior results in patient outcomes (survival and toxicities) or study outcomes (trial accrual and FDA or compendium approval) compared with clinical trials that use only conventional eligibility criteria. Conflicting evidence and opinion have been voiced, in part because of a flaw in thinking.11-13 The availability of clinical trials is highly variable, and it is dependent on the number and types of trials active at any given time in a research portfolio and the resources and capabilities to support clinical trial research at the oncology practice site to which the patient has access. Attempting to measure the value of NGS testing in isolation of these dependencies is certain to generate conflicting experiences.

**Patient Treatment**

The National Academy of Medicine report defined clinical utility as “evidence of improved measurable clinical outcomes and [a test’s] usefulness and added value to patient management decision-making compared with current management without [omics] testing.”19 The SHIVA trial was a well-designed study to evaluate the use of NGS combined with copy number and immunohistochemistry protein analysis for randomization to a molecularly driven treatment with approved drugs given off label versus standard chemotherapy treatment, irrespective of molecular characterization.14 As noted above, the impact of this study was dependent on the molecularly driven therapeutic choices that were available, which were limited to three signaling pathways (PI3K/AKT/mTOR, RAF/MEK, and hormone receptor–based) and single-agent therapy. The study failed to show benefit to biomarker-driven treatment selection within the constraints mentioned. A critical observation was that more than one molecular alteration was found in 28% of patients. The study design called for selection of a drug-target match when there was a drug that directly targeted a mutation over a drug that had an effect on a downstream signal. Although this may be a plausible strategy, other biologic considerations, such as adaptive feedback and cross talk between signal transduction pathways, that are not evident without bioinformatics tools are likely to play a major role in the selection of a drug or drug combination in the presence of multiple mutations reported by NGS testing.

The Intermountain Healthcare Multi-Institutional Molecular Tumor Board reviews NGS tests performed on patients outside the context of a clinical trial and based on preclinical and clinical published literature, issues recommendations for targeted therapies. A retrospective study of 36 patients with cancer whose cases were reviewed by the Molecular Tumor Board compared progression-free survival and cost of care of these patients with those of a contemporaneous matched control population who received standard of care biomarker testing and targeted therapy or chemotherapy per NCCN guidelines or best supportive care. Superior progression-free survival in the Molecular Tumor Board cohort was reported at 22.9 versus 12 weeks for the control cohort (HR 0.47; p = .002). Cost of care per week on therapy for a subgroup of patients for whom cost data were available was not significantly different at $4,665 for Molecular Tumor Board versus $5,000 for control (p = .126).15

**Assessment**

NGS and other genomics-based tests involve complex and rapidly changing technology. The velocity with which new technology is created and made available precludes a time-consuming guidance process, during which that technology may risk obsolescence. Instead, emphasis should be placed on the molecular laboratory processes and quality assurance programs that can be applied across test development and clinical testing. Bioinformatics and the dry laboratory component of NGS testing are critical parts of the value of NGS testing, especially because they result in clinical interpretation/annotation of the reports that provide guidance on treatment choices. Although there is a growing number of therapeutic agents either FDA approved or compendium listed, the majority of therapeutic opportunities for patients will be through clinical trials. Therefore, the value of NGS testing is linked to the capability and resources available to match a patient’s NGS test results to meaningful access to a clinical trial. As a patient’s clinical course evolves, serial monitoring and retesting will be needed to adjust treatment either at time of clinical progression or perhaps, even as resistant clones emerge before detection as clinical progression by imaging. Predictive analytics that provide guidance on when to retest and computational biology analytics that help interpret genomic mechanisms of resistance are needed.

The value of NGS can only be accurately assessed in the context of a health care delivery system and its clinical trial research enterprise. The value will vary accordingly.
PATIENTS WITH METASTATIC CANCER SHOULD HAVE THEIR TUMORS MOLECULARLY PROFILED (H. BURRIS)

Among the exciting advances in the treatment of cancer, including novel immunotherapy approaches and targeted small molecules, the ability to molecularly profile a patient’s tumor offers the opportunity to help each and every patient, researcher, and therapeutic approach. In advocating for the position of doing broad-based genomic sequencing on all patients’ tumors in the metastatic setting, benefits can be reaped for the individual subject, the clinical trials that should be considered, and all patients with cancer by gaining a better understanding of the aberrations seen across various groups.

To simply not perform molecular testing may deny patients of impactful and life-altering therapies. The regulatory premise behind the recent FDA approval of a broad-based NGS panel is that patients with a variety of cancers, including non–small cell lung cancer, melanoma, breast cancer, colorectal cancer, and ovarian cancer, may benefit from 15 different FDA-approved treatment options. Furthermore, performing a single molecular test on a patient limits the potential benefit for that individual patient to one therapeutic option, providing no information for other treatments, trials, patients, or the field as a whole.

Two very precious commodities, tissue and time, are saved by assaying for numerous analyses at once to identify possible therapeutic options, and broad-based NGS tests are more sensitive than other assays. Examples include greater sensitivity for NGS over fluorescence in situ hybridization in detecting ALK rearrangements and the identification of clinically relevant alterations in previously identified patients with “negative” non–small cell lung cancer. Additionally, it has been shown that microsatellite instability can be concurrently assessed with NGS versus polymerase chain reaction/immunohistochemistry methodology. With the recent approval of pembrolizumab for patients with microsatellite instability high tumors, regardless of histology, the urgency in identifying these patients early in decision-making is even more critical.

It is becoming increasingly evident that tumor mutational burden (TMB) will play a role in the use of the novel immunotherapies, particularly the checkpoint inhibitors. In one study across diverse tumors, patients with high TMB versus patients with intermediate or low TMB had a higher response rate (58% vs. 20%; p = .0001) and longer median progression-free survival (12.8 vs. 3.3 months; p < .0001). TMB is only assessed when NGS or whole-exome sequencing is performed. A December 2017 letter to the editor in the New England Journal of Medicine described a strong linear correlation between TMB and objective response rate across 27 tumor subtypes enrolled in clinical trials and treated with anti–PD-1 or anti–PD-L1 monotherapy. Of note, these trials did not select for patients based on PD-L1 expression.

Equally important is the potential for NGS broad-based testing to highlight treatment options where there is likely to be little benefit. These situations would include RB1 losses and mutations and ESR1 mutations in breast cancer, EGFR amplifications in lung cancer, and BRAF isofom switching mutations. Certainly, TMB low tumors may also be included in this paradigm.

Numerous examples of identifying therapeutically relevant subsets of patients undergoing NGS testing are described in the literature. In a study of the MSK-IMPACT assay in more than 10,000 patients who were metastatic receiving NGS testing, 37% had at least one clinically relevant mutation, which was defined as a finding that could be addressed with a registered clinical trial or an off-label therapy. A unique publication on 200 patients with cancer of unknown primary site using the FM1 NGS test found that nearly all patients’ tumors possessed at least one clinically relevant mutation. These potentially clinically relevant findings do not occur with routine histopathology and single-gene assays.

Over 1,000 patients with MSK-IMPACT NGS chose to have additional analysis for germline mutations. The researchers found that 182 (17.5%) carried mutations linked to cancer susceptibility. This is substantially higher than one expects to see in the general cancer populations (5%–10%) and further supports molecular profiling.

Contained within numerous phase I publications and based on my own personal experience, patients with variants of unknown significance, previously uncharacterized aberrations, or simply very rare mutations discovered through NGS have experienced dramatic benefit. The recent success with the kinase inhibitors of the neurotrophic tropomyosin receptor kinase gene rearrangements highlights these examples. Patients with neurotrophic tropomyosin receptor kinase gene fusions have experienced response rates of greater than 70%, with durable responses extending beyond a year in nearly all of those in the applicable group. NGS methods have greatly aided the development of this particular field in both the discovery of unbiased gene fusions as well as identifying appropriate patients. Current targets being explored in phase I clinical trials include AXL, IDH, METAP, EZH2, RET, and ERK among others. By and large, identifying these patients is only practical through NGS testing. Discovering which patients in various clinical settings with unique prior treatment histories and pathology have these mutations will benefit the greater good through more efficient drug development strategies.

In a similar vein, several prominent basket or umbrella trials are currently enrolling patients based on matched molecular alterations. These studies include the NCI’s MATCH, the ASCO’s TAPUR, and Sarah Cannon’s MyPathway. Almost all enrollment is through the use of broad-based NGS testing, which allows for the greatest possibility of accessing the available study agents. Analysis of these results and evaluation of the molecular profile versus the response will be invaluable for future efforts. It is likely that the next-generation of these studies will look at combination therapies with better matching and will not try to fit these unique molecular profiles into one basket or treatment. Early reports from the TRACERx trial highlight the importance of NGS testing to evaluate tumor heterogeneity head.
on and not use it as an excuse to not profile. This study is conducting multiregion, whole-exome sequencing on early-stage, resectable non–small cell lung cancer tumors. Patients are followed until relapse, at which point NGS is performed on the metastases to compare and evaluate variables for risk and location of recurrence. This approach certainly foreshadows the possibility of bringing NGS into earlier stages of disease to possibly impact adjuvant therapy.27

Molecular profiling is not a standalone technology for cancer care. Rather, it is the application of new methodologies adding uniquely to the pathologic descriptions of tumors. Established methods, such as microscopy, immunohistochemistry, and fluorescence in situ hybridization, were once investigatory and relatively expensive, while only benefiting a minority of patients on their introduction into practice. The insights that were then gained by applying them across broad populations aided in the redefinition of many tumor classifications, resulting in treatment changes for many patients. The discovery of c-erbB2/Her2 and the use of immunohistochemistry and subsequently, fluorescence in situ hybridization led to the use of trastuzumab and other Her2 inhibitors, markedly changing the prognosis for that subset of patients with breast cancer.

Cost is always an issue, and the pricing of NGS testing remains a moving target. That said, with the price of new therapies often exceeding $10,000 per cycle and the associated response assessment scans priced at several thousand dollars every couple of months, the cost to benefit ratio seems reasonable in further determining that the best therapy for the patient’s tumor is being used. Interpretation and incorporation of the molecular results into treatment decisions are another common excuse. My institution, Sarah Cannon, has merged with the bioinformatics company Genospace to provide that expertise in decision support while also matching to potential clinical trial options.

Whether it is to try and identify an appropriate clinical trial, confirm the use of an approved therapy, take a chance on finding the rare, actionable mutation, or simply add to the knowledge base for all, informed patients with cancer want their tumors to be molecularly profiled. I know that I would.

MANAGING EXPECTATIONS AND MANAGING COSTS: OPTIMIZING THE VALUE OF NGS IN CANCER CARE (L. SALTZ)

I recently received a letter from a family of a patient with colon cancer whom I do not know containing the following: “I saw a brief TV program about a clinical trial called Precision Oncology, that you are currently practicing where a patient who had tumors all over the body had taken 2 pills every day for a week and the tumors disappeared. We are desperately seeking other medical help for my father, hoping and praying that you would review his latest reports and let me know if you think you’re clinical trial will be effective?”

I do not know what program the writer is referring to, but clearly, we have to be careful not to allow or propagate the perception that “precision oncology” has reached a point where such benefits can be offered with any reasonable likelihood or frequency. Molecular profiling of tumors using NGS assays will open up some options for some people, but many and in fact, most patients with solid tumors will not be meaningfully benefited by NGS at this time. Managing expectations will involve first managing our own expectations and then helping patients understand what molecular profiling of their tumor is and what it is and is not likely to accomplish. As is always the challenge in oncology, we want to provide hope to the degree that it is realistic to do so, but we do not provide benefit and we can certainly cause harm if we provide false hope.

In addition to managing expectations, it has always been our responsibility as physicians to carefully consider cost and value in the care of our patients. In 2002, the foundations of the American Board of Internal Medicine and the American College of Physicians in conjunction with the European Federation of Internal Medicine published a Physician Charter for the new millennium outlining our professional responsibilities. One of those responsibilities reads: “While meeting the needs of the individual patients, physicians are required to provide health care that is based on wise and cost-effective management of limited clinical resources. ... The Physician’s professional responsibility for appropriate allocation of resources requires scrupulous avoidance of superfluous tests and procedures.”28 Consistent with that, I am proud to note the long-term inclusion of leadership in “cost-effective patient care” in the mission statement of my institution, Memorial Sloan Kettering Cancer Center.29

Challenges faced with introduction of any new technology into clinical practice include understanding what that technology does and does not offer and who is and is not an appropriate candidate for its use. NGS is no exception. As we advance in the era of precision oncology in general and NGS in particular, we must think carefully about what exactly it is that we are talking about, who is in a position to benefit, and what level of benefit can be realistically expected. As with all technologies, value can be maximized by appropriate use (high-value care) and curtailment of inappropriate use (low-value care).

There is no way around the reality that each assay run will entail a financial cost. Although what Medicare will pay for an NGS assessment and under what circumstances are under intense discussion at the time of this writing, currently, commercial assays are priced at approximately $5,000 to $7,000. It is important to remember that value and cost move in opposite directions if the other parameters stay stable. Thus, if the cost of NGS rises, its relative value is diminished. Conversely, if competition and market forces cause a drop in the cost of NGS, then the value rises even without a change in therapeutic efficacy. It is too early to tell in what direction this will move.

To get a sense of the costs, for the purposes of this discussion, let us use the conveniently round number of $5,000 as the cost of an assay, recognizing that higher fees may be charged and lower amounts may be paid depending on contracts between providers and payers. That is the cost to run...
the assay a single time. If assays are run on multiple occasions on a single patient, then the cost will go up accordingly, and at least based on current practice standards, the value will go down. Previously, the constraints of undergoing tumor biopsy limited the number of times that NGS would be performed. The advancing technology of liquid biopsy changes this and makes it easy to perform an assay more frequently. We must ask whether we should do repeat biopsies, and if so, how often? A $5,000 assay once may sound like a relatively small amount. As the number of such biopsies per patient increases, that amount increases accordingly. If we do one NGS assay on each of the roughly 600,000 new patients with metastatic cancer each year, that brings us to an annual expenditure of $3 billion. This, of course, does not include the cost of additional biopsies if those are performed. In most cases, actionable mutations will be present in the primary tumor and archived tissue samples. Rebiopsy is rarely indicated and constitutes added risk and considerable added expense.

Taken in the context of the overall cost of care, this may seem relatively modest. However, much of the cost has to do with what path this information takes us down. If a truly actionable pathway is identified and truly active drugs are able to be obtained and administered, then the cost to benefit ratio will be low, and the value of the intervention will be high. If, however, an unproductive course of action is pursued, such as prescribing an MEK inhibitor for an identified RAS mutation or a combination of expensive drugs based on laboratory data without clinical evidence, then the opposite, high cost to benefit ratio and low-value care, will have resulted.

How might we approach a sustainable strategy to provide NGS tumor evaluation where needed, maximize the chance that all who can benefit from this technology do, and at the same time, avoid depleting resources through nonvalue-added use? If used to identify a known active agent for a particular mutational profile, then the likelihood of improved outcome and improved value is high. This is consistent with the current language that the Centers for Medicare and Medicaid is proposing for coverage of NGS assays for Medicare beneficiaries.30 As of the time of this writing (subject to public comment and not yet finalized), the proposal is to cover an NGS assay that is FDA approved for Medicare beneficiaries who fulfill the following criteria: (1) have recurrent, metastatic, or advanced stage IV cancer; (2) have not been previously tested using the same NGS assay; and (3) have decided to seek additional cancer therapy. The language further goes on to say that results from this test must be used in the treatment of the patient, including guiding selection of treatments proven to improve health outcomes. It should be noted that we cannot regard a treatment as “proven to improve health outcomes” for patients on Medicare unless the Centers for Medicare and Medicaid agrees to cover it, and what the Centers for Medicare and Medicaid covers is either an FDA-approved indication or a Compendium-listed indication.

There is additional language from the Centers for Medicare and Medicaid proposing coverage “with evidence development,” which would potentially allow for screening for clinical trials within the National Institutes of Health-National Cancer Institute clinical trials network. Although I would hope that this would be expanded in the final determination to cover other trials as well, at present, this questions remains unsettled. Furthermore, such an approach would not provide coverage for drugs putatively identified as being useful on the basis of the NGS assay outside of a clinical trial, unless treatment of that particular mutational pattern and tissue type is recognized by either the FDA or a recognized compendium. We can anticipate much frustration in a patient in whom an NGS assay suggests a course of action but for whom a trial is unavailable and coverage for the identified targeted agent is not forthcoming. This is and will remain a challenge as the use of NGS tumor profiling broadens.

Use of information to identify patients most appropriate for participation in a clinical trial that is specifically targeting a mutation or mutational profile would be expected to add considerable value, hopefully, to the patient and at least to the research effort to define better treatments. If, however, an NGS assay was to be obtained and used in patients who were not candidates for such treatments, it would be adding cost and expense without adding benefit, thereby lowering value. Virtually all clinical trials require a performance status (PS) of Eastern Cooperative Oncology Group (ECOG) 0 to 1. A few may allow patients who have an ECOG PS of 2. For patients with a PS 3 or 4, there are no clinical trials. This is because the chance of benefit drops considerably and the chance of harm rises considerably with declining performance status. Similarly, those patients with elevated bilirubin or creatinine or low platelets, neutrophils, or hemoglobin are not realistic candidates for clinical trials. The performance of an NGS assay for the purpose of finding a trial for a trial-ineligible patient would result in added expense and virtually no benefit.

In 2017, there were approximately 1.6 million new cancers diagnosed and 600,000 cancer deaths. Because most cancer deaths are the result of metastatic disease, we can see from these numbers that, of the patients with cancer, a substantial percentage has earlier-stage disease. For most tumors at this time, NGS would provide little if any usable information for patients with early-stage cancer. For example, in patients with colorectal cancer, genotyping for RAS and BRAF mutational status is absolutely necessary to provide appropriate treatment of metastatic disease, but it is not useful for patients with stage I, II, or III disease. Similarly, patients with early-stage cancer are not appropriate for consideration of novel clinical trials of unproven agents. As such, outside of a research setting, the expense of NGS genotyping would not be warranted in these patients at this time.

Exceptions may exist, and more may develop as data mature. NGS can effectively be used for determination of mismatch repair status, a question that is relevant in patients with stage II colorectal cancer for decisions regarding consideration of adjuvant therapy and screening for Lynch syndrome, a question that is relevant for all patients with colorectal cancer. If,
however, a patient’s tumor is determined to be microsatellite stable by routine polymerase chain reaction or mismatch repair proficient by immunohistochemistry, then performing an NGS assay to look for mismatch repair deficiency would be redundant and of little or no value. If the expense of immunohistochemistry or polymerase chain reaction is saved by only doing NGS for the determination of microsatellite instability, then the cost of the NGS is at least partially offset, and the value of such a maneuver is increased. To the degree that newer technologies can replace, rather than be added on to, older technologies, these newer technologies become more cost effective.

CONCLUSION

As we work to maximize benefit from NGS tumor profiling, we have to both keep a reasonable perspective on what can be expected from this technology and help our patients to maintain reasonable expectations as well. We have good reason to believe that this technology has the potential to improve outcomes for many people with cancer. We must get that message out while maintaining a balance of optimism and realism, without which it is easy for patients and their families to build up expectations far beyond what can be delivered.

References


CENTRAL NERVOUS SYSTEM TUMORS
 Integrating Genomics Into Neuro-Oncology Clinical Trials and Practice

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OVERVIEW

Important advances in our understanding of the molecular biology of brain tumors have resulted in a rapid evolution in the taxonomy of central nervous system (CNS) tumors, which culminated in the revised 2016 World Health Organization classification of CNS tumors that incorporates an integrated molecular/histologic diagnostic approach. Our expanding understanding of brain tumor genomics and molecular evolution during the disease course has started to impact clinical management. Furthermore, incorporation of genomic information in ongoing and planned neuro-oncology clinical trials is expected to lead to improved outcomes and result in personalized treatment options for patients with CNS malignancies.

Over the last 30 years, widespread efforts to characterize chromosomal abnormalities, genomic mutations, epigenetic alterations, and proteomic changes in cancer cells have rapidly increased our understanding of the molecular biology of neoplasia. These advances have challenged the histology-centric paradigm of tumor classification, demanding a reassessment of current diagnostic algorithms and categories and development of novel strategies for incorporating molecular and genetic data into the nosology of neoplasia. A new paradigm is emerging, highlighted by the publication of the 2016 World Health Organization Classification of Tumors of the Central Nervous System, which adopts, for the first time, diagnoses that integrate both histologic and molecular parameters. Application of these recent changes in the criteria and taxonomy of CNS tumors and in clinical practice results in both challenges and opportunities that are many and varied.

HISTOLOGIC CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

Systematic attempts to establish a universal taxonomy for CNS tumors began in the 1950s with the groundbreaking Armed Forces Institute of Pathology and Union for International Cancer Control texts. These efforts were, however, not met with widespread international acceptance. Subsequently, World Health Organization (WHO) working groups were established to define international diagnostic standards. The first meetings of a CNS-focused group convened in 1970, culminating in the first WHO “blue book” for CNS tumors that was published in 1979. Similar to classification schemes in other organ systems, the WHO classification of CNS tumors has typically been organized by the presumed histogenesis of tumors ascertained through morphology and immunohistochemistry (e.g., astrocytic, oligodendroglial, or ependymal tumors). Notably, in contrast to the staging of other solid tumors, which relies on the TNM classification system, typically based on tumor size and extent of spread, prognostic information for CNS tumors is conveyed using a “WHO grade” designation. Grading is based on histologic characteristics such as mitotic rate or vascular proliferation, which have more prognostic value for CNS tumors than does tumor size or extent of invasion. Numerous clinicopathologic studies have driven the iterative and continual refinement of WHO diagnostic categories and these changes have been codified in new editions and revisions of the WHO CNS manual in 1993, 2000, 2007, and 2016.

INTEGRATED MOLECULAR CLASSIFICATION OF CENTRAL NERVOUS SYSTEM TUMORS

In addition to numerous advances in the histologic classification of CNS tumors in each subsequent edition of the WHO manual, investigators across the field of neuro-oncology have uncovered distinct patterns of recurrent genomic alterations in many CNS neoplasms. Such molecular and genetic findings were included in the 2000 and 2007
WHO classifications, but at the time, these were considered as supplemental to the histologic diagnoses. However, as the number of findings has increased and clinicopathologic analyses have matured, the International Society of Neuropathology and WHO working group surveys supported inclusion of molecular criteria in tumor classification with the aim of increasing diagnostic reproducibility and improving patient care. These insights were incorporated into the 2016 revision of the WHO classification. The most substantial changes were in the classification of diffuse gliomas and embryonal tumors, which provide illustrative examples of the new paradigm of integrated molecular classification.

Diffuse Gliomas

Since their first classification by Bailey and Cushing,16 diffuse gliomas have been classified by their presumed lineage differentiation (astrocytic or oligodendroglial) based on morphologic features. Oligodendrogliomas were among the first CNS tumors in which specific molecular genetic alterations were recognized, with the identification in 1994 of the codeletion of chromosomal arms 1p and 19q.17 Further studies showed improved outcome and response to chemotherapy in tumors with these alterations, providing tantalizing proof-of-principle evidence that specific molecular alterations may be simultaneously diagnostic, prognostic, and predictive of treatment response.18 In 2008, integrated genomic analysis identified recurrent mutations in the isocitrate dehydrogenase genes (IDH1/2), most commonly the IDH1 R132H mutation, in nearly all secondary glioblastomas. Subsequent studies showed that these mutations were also present in the majority of low-grade astrocytomas and oligodendrogliomas. Clinical correlation showed that these mutations are highly predictive of long-term prognosis.19,20

Additional work identified alpha-thalassemia/mental retardation syndrome X-linked (ATRX) mutations in astrocytomas and secondary glioblastomas, which frequently co-occur with mutations in tumor protein 53 (TP53).21

Such advances suggested that the integration of genotypic findings may provide more biologically relevant diagnostic categories, such as the presence of 1p/19q codeletion and IDH1/2 mutations for oligodendroglioma; of TP53, ATRX, and IDH1/2 mutations for astrocytomas and secondary glioblastomas; and of epidermal growth factor receptor (EGFR) amplification and CDKN2A/2B deletion among other aberrations for primary glioblastomas.22 Clinicopathologic and molecular studies to explore this possibility showed that integrated molecular data provided superior prognostic significance than traditional histologic classification alone.23,24 For example, detection of the 1p/19q codeletion in morphologically defined oligoastrocytomas or oligodendrogliomas was associated with clinical outcomes more concordant with genotype rather than histologic phenotype or grade.

Thus, targeted gene sequencing and copy-number analysis is becoming increasingly essential for the proper classification of most brain tumors. For gliomas, including the most common malignant glioma diagnosis (i.e., glioblastoma), a complete workup requires IDH mutation assessment by immunohistochemistry using antibodies that recognize the IDH1 R132H mutant protein (Fig. 1) and/or mutation hotspot sequencing that can identify alternative IDH1 mutations such as R132C or IDH2 mutations. Glioblastomas are divided in the 2016 WHO classification of CNS tumors into (1) glioblastoma, IDH-wild type (approximately 95% of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients older than age 5525; (2) glioblastoma, IDH-mutant (approximately 5% of cases), which frequently corresponds to secondary glioblastoma with a history of prior lower-grade diffuse glioma and preferentially arises in younger patients25; and (3) glioblastoma, not otherwise specified, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed. The definition of full IDH evaluation can differ for older patients with glioblastoma relative to younger adults with glioblastoma and relative to WHO grade II and grade III diffuse gliomas. In the latter situations, IDH sequencing is highly recommended following negative R132H IDH1 immunohistochemistry, whereas the near absence of non-R132H IDH1 and IDH2 mutations in glioblastomas from patients older than approximately age 55 suggests that sequencing may not be needed in the setting of negative R132H IDH1 immunohistochemistry among such patients.27 In the case of oligodendroglioma and oligoastrocytomas, in addition to IDH mutation, testing for 1p/19q deletion by fluorescence in situ hybridization, array comparative genomic hybridization, or next-generation sequencing is also needed. Accordingly, institutions that do not offer such molecular testing will frequently be required to request testing from outside laboratories.

Assays that characterize both mutations and copy-number alterations, such as targeted next-generation sequencing,

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**PRACTICAL APPLICATIONS**

- The 2016 World Health Organization classification of CNS tumors resulted in a major restructuring of some of the most common CNS tumors, including glioma and medulloblastoma.
- Characterization for IDH mutations is now required as part of the histologic characterization of diffuse gliomas.
- The presence of both 1p/19q codeletion and IDH mutations is necessary for the diagnosis of oligodendroglioma to be established, and it is impacting the standard-of-care treatment of these patients.
- The recognition of the molecular evolution and transformation of gliomas during the disease course highlights the importance of repeat biopsies at recurrence.
- A number of ongoing clinical trials for tumors such as glioma, medulloblastoma, meningioma, and craniopharyngioma are using biomarker-based and adaptive designs that are expected to result in the development of personalized treatment approaches for patients with primary CNS tumors.
provide an efficient approach for capturing the data needed for glioma classification as well as for identifying a wide range of other aberrations that occur at low frequency but that may inform tumor classification, patient care, and clinical trial decisions such as *BRAF* V600E mutations, histone gene mutations, *FGFR* fusions, and a range of focal amplifications or deletions. For instance, recurrent mutations in histone H3 genes define an infrequent entity codified in the 2016 WHO classification as H3K27M-mutant diffuse midline glioma. This mutation is thought to result in dysregulation of polycomb repressor complex 2 (PRC2) with resultant genome-wide epigenetic alterations. These tumors may exhibit histologic features of a high-grade (Fig. 2A) or low-grade (Fig. 2C) glioma and may be identified in most cases by immunohistochemistry specific for mutated histone H3F3A when suspected clinically (Fig. 2B and D), but they can also be identified by sequencing technologies when they occur in atypical presentations. Although both high- and low-grade histologic phenotypes are thought to carry a dismal prognosis based on current clinicopathologic data and are correspondingly classified as WHO grade IV, further assessment of the prognostic and predictive value of such histologic features in cohorts of molecularly characterized cases is underway and may reveal stratification of outcomes based on histologic phenotype.

**Medulloblastoma**

The 2007 WHO classification defined multiple histopathologic variants of medulloblastoma with different clinical outcomes. Systematic transcriptomic, microRNA, cytogenetic, and epigenomic studies sought to understand the differences between subtypes and had established by 2012 that multiple biologically distinct genotypic clusters could be defined with excellent cross-modality concordance, including those with activation of the Sonic hedgehog signaling pathway (SHH) or Wnt pathways. Clinicopathologic studies subsequently showed that distinct biologic clusters had different clinical outcomes. For instance, there was an excellent prognosis for Wnt pathway-driven tumors, intermediate prognosis for SHH pathway-driven tumors and poor prognoses for non-SHH/WNT tumors: these genotypic clusters frequently, but not always, correlated with specific histologic categories.

The revised 2016 WHO classification for the first time incorporates these advances into integrated diagnoses. Tumors are substratified into four histologic categories (classic, desmoplastic/nodular, extensive nodularity, and large cell/anaplastic) and four principle molecular categories (WNT-activated, SHH-activated, group 3, and group 4), allowing for treatment and prognostic stratification by pathway activity and histology. As with the grading of diffuse gliomas, histologic descriptors remain useful for the diagnosis of medulloblastoma. Nearly all medulloblastomas with desmoplastic/nodular or extensive nodularity histology fall into the SHH-activated molecular group; these tumors have lower risk profiles and may be eligible for trials of hedgehog pathway inhibitors. WNT-activated tumors, a particularly low-risk group, nearly always exhibit classic histology. Anaplastic/large cell tumors are typically SHH-activated or group 3 tumors, and these tumors are associated with poor prognosis.

**Other Tumors**

In addition to the examples listed above, the revised 2016 WHO classification includes several other molecularly defined entities, including *RELA* fusion-positive ependymoma and embryonal tumor with multilayered Rosettes, *C19MC*-altered. These entities follow a similar paradigm as described above, and extended discussion may be found elsewhere. In addition, a “not otherwise specified” classification was added for lesions with atypical genotypes or cases lacking molecular data.
EVOLVING PARADIGMS AND FUTURE DIRECTIONS IN BRAIN TUMOR HISTOLOGIC CLASSIFICATIONS

The integrated diagnoses in the 2016 WHO classification incorporate a large number of canonical molecular alterations; however, the theoretical limit of biologic findings that may have clinical relevance is vast. Integrated molecular diagnoses may see a rapid expansion as novel assays expand the scope of genetic, molecular, and phenotypic profiling. Recent years have seen an explosion of genome-level sequencing data whose clinicopathologic contextualization is still in its infancy, and rapid advances in epigenomic and proteomic profiling and acute sensitivity testing approaches promise to enable far greater granularity of tumor classification. Glioblastomas, for instance, may prove to be effectively substratified for prognostication or clinical treatment by the presence of specific pathway alterations or combinations of alterations (e.g., *EGFR* amplification), epigenetic profiles such as the glioma CpG island methylator phenotype (G-CIMP) or *O-6-methylguanine methyltransferase (MGMT)* promoter methylation (a prognostic and possibly predictive factor), and numerous other as-yet undiscovered alterations. To address this complexity, future classification systems may alternatively seek to develop diagnoses with succinct condensations of the most clinically relevant features, or exploit computational methods to develop increasingly high resolution “precision” classification and treatment plans for each unique tumor. As in the taxonomy of all tumor types, the challenge for brain tumors will also be in establishing the merits of when to “lump” or “split.”

Recent years have seen an explosion of genome-level sequencing data whose clinicopathologic contextualization is still in its infancy, and rapid advances in epigenomic and proteomic profiling and acute sensitivity testing approaches promise to enable far greater granularity of tumor classification. Glioblastomas, for instance, may prove to be effectively substratified for prognostication or clinical treatment by the presence of specific pathway alterations or combinations of alterations (e.g., *EGFR* amplification), epigenetic profiles such as the glioma CpG island methylator phenotype (G-CIMP) or *O-6-methylguanine methyltransferase (MGMT)* promoter methylation (a prognostic and possibly predictive factor), and numerous other as-yet undiscovered alterations. To address this complexity, future classification systems may alternatively seek to develop diagnoses with succinct condensations of the most clinically relevant features, or exploit computational methods to develop increasingly high resolution “precision” classification and treatment plans for each unique tumor. As in the taxonomy of all tumor types, the challenge for brain tumors will also be in establishing the merits of when to “lump” or “split.”

In the context of evolving classification systems, the establishment of clinical practice guidelines by the Society for Neuro-Oncology and the College of American Pathologists will foster the appropriate level of genetic testing for patients with brain tumors.

Given the superiority of molecular analyses in discriminating a variety of lesions, an important question is whether histologic evaluation of tissue will remain necessary. We believe that histologic review will still be required for the foreseeable future. First, histologic evaluation of specimens remains the most efficient and accurate methodology for the initial diagnosis of neoplasia and is essential for determining the tissue regions most amenable to molecular profiling. Although molecular studies may become more precise at identifying specific cellular classifications of tumors, including possible epigenetic identification of tumor cell lineage, histologic evaluation of tissue also reveals spatial information that is not available by molecular studies, such as the...

FIGURE 2. H3K27M-Mutant Diffuse Midline Glioma

(A and B) Hematoxylin and eosin–stained section (A) of an H3K27M-mutant diffuse midline glioma in the thalamus displaying high-grade morphology supported by immunohistochemistry (B) using an H3K27M mutation–specific antibody (brown staining). (C and D) Hematoxylin and eosin–stained section (C) of an H3K27M-mutant diffuse midline glioma displaying low-grade morphology in the cingulate gyrus supported by immunohistochemistry (C) using an H3K27M mutation–specific antibody (brown staining).
spatial relationships between tumor cells and subgroups of immune cells may become increasingly important in the age of high-dimensional pathology. In addition, as illustrated by the present grading of diffuse gliomas, histologic features may retain superior diagnostic utility in specific situations, although continued analysis of genomic or epigenetic alterations may reveal more effective paradigms.

TISSUE ACQUISITION BEFORE, DURING, AND AFTER TREATMENT: INCORPORATING GENOMICS INTO NEURO-ONCOLOGY PRACTICE

The 2016 WHO classification of CNS tumors incorporates and mandates genomic analysis in routine neuropathology and neuro-oncology practice. There are two associated challenges, however. First, this improved classification paradigm applies primarily to initial diagnosis: the impact of treatment interventions on these molecular markers remains poorly characterized. Second, additional molecular alterations of prognostic or predictive significance (MGMT methylation in glioblastoma, V600E mutation in gliomas, TSC mutations in subependymal giant cell astrocytoma, etc.) were not included. Furthermore, this classification was only in part able to capitalize and include existing information on genetic, transcriptional, and epigenetic changes, which occur during glioma evolution. Therefore, serial tissue acquisition to guide clinicians in tailoring treatment to the dynamic changes seen in the tumor through the continuum of care is increasingly becoming a clinical mandate. Available technology, including next-generation sequencing, which is increasingly available for clinical use, can ensure that the clinician’s knowledge of the biology of the tumor is at least as up to date as the dynamic changes occurring in these malignancies and can create the foundation for future therapeutic advances. We anticipate that this approach could hold the greatest immediate impact in the treatment of patients with glioma.

A substantial body of existing evidence supports that recurrent gliomas undergo transformation and clonal evolution. For example, Riehmer et al. used genome-wide array comparative genomic hybridization analysis and showed that 75% of non-IDH mutant recurrent glioblastomas in their series acquired new genomic aberrations while either maintaining or losing their primary tumor aberrations, referred to as sequential and discrepant pairs, respectively. Similarly, recent work by Johnson et al. comparing 23 matched primary to recurrent lower-grade gliomas by genome sequence analysis found an average of 33 somatic mutations in each primary tumor, of which only an average of 54% were also detected in the matched recurrent tumor. Of these reported somatic mutations, only the prognostically favorable IDH mutation was shared in every matched recurrent case, suggesting that IDH mutation remains intact through serial tissue acquisition. Because IDH mutation is believed to be an early initiation event in gliomagenesis and is maintained through serial tissue acquisition, downstream molecular alterations tightly coexpressed with IDH mutation, such as 1p/19q codeletion, ATRX, and TP53 mutations, are also shared in most but not all cases, despite treatment and tumor recurrence. In contrast, genomic events that occur later in glioma evolution, such as aberrations in receptor tyrosine kinases platelet-derived growth factor receptor A and EGFR, as well as phosphatase and tensin homolog (PTEN) mutation, have been reported to “switch” with tumor progression due to divergent clonal selection and their predominantly mutually exclusive presence in glioblastoma cells. Of practical importance, in the series by Johnson et al., exposure of these patients with low-grade glioma to the commonly used chemotherapeutic agent temozolomide resulted in the acquisition of mutations in the DNA mismatch-repair pathway and the development of a hypermutated phenotype.

In addition to the information gathered from bulk tumor analysis, important information can be derived from rapidly evolving state-of-the-art technology that now allows for genomic profiling of single cells derived from a bulk tumor. Results from the single-cell-omics approach in gliomas support that primary tumors represent a heterogeneous group of subclones that, upon treatment, undergo selective pressure resulting in divergent clonal evolution at recurrence. This theory highlights the importance of developing clonal-specific treatments, as opposed to a bulk “one-stop-fits-all” paradigm, and can better explain primary and secondary resistance to chemotherapy. For example, Meyer et al. demonstrated that treatment-naïve patients with glioblastoma harbor temozolomide-resistant clones regardless of MGMT promoter status. This may explain the variability of responses to temozolomide even within this predominantly sensitive group.

Taken together, these studies suggest that genomic evolution of recurrent gliomas could impact treatment decisions, including eligibility for targeted therapies or combinations, and support the rationale for tissue acquisition at recurrence. In conjunction with tissue-deriving information, ongoing research on liquid biopsies from blood or cerebrospinal fluid, which characterize genetic material in exosomes or circulating DNA, and advanced imaging, including functional or metabolic imaging, can create the foundation for the development of reproducible noninvasive measures for monitoring molecular evolution in gliomas (Fig. 3).

INTEGRATING TUMOR GENOMICS INCLUDING WHO GUIDELINES INTO NEURO-ONCOLOGY CLINICAL TRIAL DESIGN

Diffuse Astrocytic and Oligodendroglial Tumors

Glioblastoma. Both the 2016 WHO classification of CNS tumors and our expanding knowledge of CNS tumor genomics are impacting neuro-oncology clinical trial design for many primary CNS tumors. The 2016 WHO classification of CNS tumors resulted in a major restructuring of diffuse gliomas with incorporation of genetically defined entities. As such, ongoing and future glioma trials must comply with this classification. For glioblastoma trials,
the impact overall is expected to be minor: the new classification introduces tumor characterization for the IDH status; nevertheless, less than 5% of glioblastomas harbor IDH mutations and as such, it is unlikely that the addition of this diagnostic criterion, even during the conduct of ongoing randomized trials, will impact results or imbalance groups.

Despite the fact that it was not included in the 2016 WHO classification, MGMT methylation status at diagnosis represents a prognostic and possibly predictive factor for patients with glioblastoma. Methylation of the promoter of MGMT, a DNA repair enzyme, leads to decreased enzyme activity and impaired ability to repair temozolomide-induced DNA methylation. This is important because temozolomide in combination with radiation therapy is currently the standard-of-care treatment regimen for newly diagnosed glioblastoma based on the results of the EORTC/NCIC CE3 randomized phase III trial. Retrospective analysis in a subgroup of 206/572 study patients for whom baseline tumor samples were available demonstrated that patients with MGMT promoter methylation were more likely to benefit from the addition of temozolomide. Long-term results of this trial showed that MGMT promoter methylation status was the strongest predictive factor for survival. At 3 and 5 years, 27.6% and 15.8%, respectively, of patients with MGMT methylation who received combination treatment were alive compared with 11.1% and 8.3% of patients without MGMT methylation who received combination treatment. For patients treated with radiation alone, MGMT promoter methylation was associated with a 7.8% and 5.2% survival at 3 and 5 years, respectively, whereas no patient without MGMT methylation survived beyond 3 years. Analysis of progression-free survival showed an advantage only for patients whose tumor had a methylated MGMT promoter and who were treated with temozolomide and radiotherapy (RT). These data support the prognostic value of MGMT methylation for patients with newly diagnosed glioblastoma and a possible predictive value because it impacted progression-free survival after temozolomide therapy, but the impact on overall survival did not reach statistical significance. A number of subsequent phase III trials, including RTOG 0525, RTOG 0825, and AVAGLIO, confirmed the prognostic value of MGMT methylation: patients without MGMT methylation have a median survival ranging from 14 to 16.2 months, whereas patients with MGMT methylation have a median survival ranging from 22 to 26 months. As such, stratification based on MGMT status is viewed as mandatory in newly diagnosed glioblastoma trials because imbalance of this prognostic factor can confound the results.

In addition, MGMT promoter methylation can lead to greater sensitivity of glioma cells to other agents such as PARP inhibitors that also block DNA repair. Based on preclinical data confirming that the PARP inhibitor veliparib statistically significantly enhanced the efficacy of temozolomide in patient-derived glioblastoma xenografts with MGMT promoter methylation, MGMT promoter methylation is used as an eligibility criterion for A071102 (NCT02152982), a biomarker enrichment design–based phase II/III Alliance clinical trial evaluating temozolomide/veliparib versus placebo in the adjuvant treatment of patients with newly diagnosed glioblastoma. This trial uses a marker by treatment interaction seamless phase II/III design and has currently progressed to the randomized phase III stage.

Despite the minimal clinical progress with only three new therapies having been approved by the U.S. Food and Drug Administration for the treatment of glioblastoma in the last 15 years (temozolomide, bevacizumab, and Optune), substantial molecular knowledge has been gained as a result of large-scale genome sequencing projects such as The Cancer Genome Atlas. In parallel, many new therapies have been developed for clinical testing. These advances lead to optimism that molecularly based precision medicine may improve outcomes for patients with glioblastoma, but they also highlight the limitations of current clinical trial designs that do not test multiple therapies and biomarker combinations simultaneously. At least two clinical trials in glioblastoma are attempting to address this gap: INSIGHT (Individualized Screening Trial of Innovative Glioblastoma Therapy) is ongoing and AGILE (Adaptive Global Innovative Learning Environment for Glioblastoma) is in the late planning stages. In both trials, comprehensive multiplex genomic analysis will be conducted for each patient to identify biomarker signatures prior to treatment assignments. For example, for the INSIGHT trial, initial biomarker classifiers are based on four specific pathway markers: EGFR amplification mutation; PI3K...

FIGURE 3. Workflow Demonstrating an Optimal Future Diagnostic and Treatment Selection Paradigm for Patients With Glioma in the New Molecular Era

- **MONITORING: serial MRI/function imaging**
- **MONITORING: serial liquid biopsies**
- **CONCORDANT IMAGING/LIQUID SUGGESTING RECURRENCE, REPEAT SURGERY FOR CYTOREDUCTION AND GENOMIC PROFILING**
- **BULK AND SINGLE CELL GENOMIC PROFILING**
- **PATIENT IS PROVIDED TAILORED SALVAGE THERAPY ACCORDING TO NEW GENOMIC PROFILE**
- **RECURRENT**
- **REPEAT SURGERY**
- **MOLECULAR HISTOPATHOLOGY**
- **ADJUVANT TREATMENT**
- **MOLECULAR HISTOPATHOLOGY**
- **ADJUVANT TREATMENT**
- **UPFRONT SURGERY FOR TISSUE DIAGNOSIS AND MAXIMAL SAFE RESECTION**
- **BULK AND SINGLE CELL TUMOR SEQUENCING FOR GENETIC CHARACTERIZATION**
- **PATIENT IS PROVIDED TAILORED CHEMORADIATION ACCORDING TO GENOMIC PROFILING**
- **BASELINE LIQUID BIOPSY**
- **PATIENT PRESENTATION**

[Diagram showing workflow]

- **UPTAKE:**
  - **MRI/IMAGING**
  - **BIOPSY**
  - **LIQUID BIOPSY**

- **OUTCOME:**
  - **SURGERY**
  - **CHEMORADIATION**
  - **MOLECULAR PROFILING**

- **DECISIONS:**
  - **TAILORED TREATMENT**
  - **ADVANCED TREATMENT**

- **FOLLOW-UP:**
  - **RECURRENT**
  - **REPEAT SURGERY**
  - **MOLECULAR HISTOPATHOLOGY**
  - **ADJUVANT TREATMENT**

- **OUTCOMES:**
  - **CONCORDANT IMAGING/LIQUID SUGGESTING RECURRENCE, REPEAT SURGERY FOR CYTOREDUCTION AND MOLECULAR PROFILING**
  - **BULK AND SINGLE CELL GENOMIC PROFILING**
  - **PATIENT IS PROVIDED TAILORED SALVAGE THERAPY ACCORDING TO NEW GENOMIC PROFILE**
activation (PTEN loss through analogous deletion or mutation plus deletion), PI3KCA mutation, or PIK3R1 mutation; p53 status (MDM2-4 amplification or p53 wildtype); and CDK (CDK4/6 amplification or CDKN2A disomy). Both trials follow Bayesian adaptive designs, which allow continuous evaluation of a priori biomarker hypothesis and associations with drug efficacy, with subsequent adaptation of randomization should an association be found. In the AGILE trial, which targets both patients with newly diagnosed and recurrent glioblastomas, effective therapies identified in this first learning stage will also transition in an inferentially seamless manner to a second confirmatory stage that uses fixed randomization to confirm findings and support regulatory registration. These trial designs could potentially have substantial applicability in the development of personalized treatments for patients with glioblastoma and could expedite new drug development.

**Oligodendroglioma.** The diagnosis of oligodendroglioma and anaplastic oligodendroglioma according to the 2016 WHO classification requires demonstration of both an IDH gene family mutation and combined whole arm losses of 1p and 19q (1p/19q codeletion). The RTOG 9402 and EORTC 26951 trials convincingly demonstrated that 1p/19q codeletion is both a prognostic factor as well as a predictive factor of the efficacy of procarbazine, CCNU, and vincristine (PCV) chemotherapy, administered either prior to or following radiation for newly diagnosed patients. For example, the addition of PCV led to doubling of overall survival for these patients (from 7.3 years in the RT-only group to 14.7 years in the RT/PCV group) and increased progression-free survival (from 2.9 years in the RT group to 8.4 years in the RT/PCV group) in RTOG 9402, establishing a new standard of clinical care for these patients. IDH mutation was also predictive of response. Importantly, survival and progression-free survival curves in these two anaplastic oligodendroglioma studies were identical to RTOG 9802, a trial for patients with high-risk, low-grade glioma with similar treatment arms as in RTOG 9402, supporting that genotyping in this context is more important than grade in determining prognosis and therapy efficacy. These data, which have clearly associated 1p/19q and IDH mutations with both a better prognosis as well as chemotherapy efficacy, have played a critical role in shaping the design of the CODEL trial/Alliance N0577 (NCT00887146), an international intergroup trial conducted by Alliance for Clinical Trials in Oncology, NRG Oncology, the Eastern Cooperative Oncology Group, and the Cooperative Trials Group for Neuro-Oncology. This trial started as a three-arm study comparing RT/PCV versus RT versus single-agent temozolomide among patients with 1p/19q codeleted anaplastic glioma. Based on evolving molecular and clinical knowledge gained from the RTOG 9402, EORTC 2695, and RTOG 9802 trials and the 2016 WHO classification, the N0577 trial has now modified eligibility rules that allow enrollment of all patients with oligodendroglioma, 1p/19q codeleted and IDH mutant, independent of grade. In its current design, the N0577 trial randomly assigns patients to RT followed by PCV versus RT with temozolomide followed by temozolomide and represents a prime example of how our evolving knowledge in tumor genomics can inform and alter clinical trial design in neuro-oncology.

**Medulloblastoma**

The 2016 WHO classification of CNS tumors has led to major restructuring of medulloblastomas with the incorporation of genetically defined entities that describe subgroups with distinct molecular characteristics, demographics, and prognosis. Use of this classification in clinical trials is expected to both increase the likelihood of informative results, because by definition clinical trial populations in medulloblastoma trials will be more homogenously defined, and also allow investigators to better tailor development of new treatments. Aggressive treatments with high toxicity should be reserved for subgroups with poor prognosis (e.g., group 3 or 4) in which the outcomes remain dismal, although a potential decrease of treatment intensity could be acceptable in groups such as WNT that have excellent prognosis in order to mitigate unnecessary exposure to short- and long-term treatment-related side effects. In addition, this new classification encourages incorporation of targeted treatments for groups where such treatments exist. For example, an ongoing St. Jude trial (A Clinical and Molecularly Risk-Directed Therapy for Newly Diagnosed Glioblastoma, NCT01878617) uses both a clinical risk and a molecular subtype–based classification to customize treatment of patients with medulloblastoma, including use of a targeted agent, the SHH pathway inhibitor vismodegib for patients in the SHH subgroup.

**Other Tumor Types**

Despite the fact that they are not included in the 2016 WHO classification, a number of driver mutations have been identified in other primary brain tumors, creating hope for effective targeted treatments. One such example is meningiomas, which represent the most common primary brain tumors among adults, with an incidence of 140,000 cases in the United States. Although surgery represents the mainstay of treatment of these tumors, there is a high risk of recurrence ranging from 20% for grade I up to 80% for grade III tumors, even following gross total resection. For tumors that are refractory to RT and surgery, no medical treatment has been shown to be of proven benefit.

NF2 inactivation represents the most common alteration observed in approximately 50% of meningiomas, whereas other less common alterations include AKT mutations (5%-13% of meningiomas) with 15% of meningiomas exhibiting PI3K/AKT1/mTOR pathway activation. In addition, approximately 5% of meningiomas, especially skull base, olfactory groove meningiomas, can harbor SMO mutations. Mutations in TRAF7, a proapoptotic ubiquitin ligase, were also identified in approximately one-quarter of these tumors in one study, but the role of the TRAF7 mutations in the pathogenesis of meningioma is less clear.

Based on this information, the Alliance for Clinical Trials in Oncology launched an umbrella trial (Alliance A071401, NCT02523014) in which tumors of patients with recurrent
malignant meningioma are sequenced and, depending on the predominant genetic alteration, patients are assigned to one of three treatment arms: (a) patients with NF2 mutations are treated with a FAK inhibitor, based on data supporting a synthetic lethal relationship of FAK inhibition in the context of Merlin (NF2 gene product) deficiency,72 (b) patients with AKT mutations are treated with an AKT inhibitor, whereas (c) patients with SMO or PTCH mutations are treated with a SMO inhibitor. The fact that these driver genetic alterations are mutually exclusive increases the enthusiasm for the therapeutic potential of this approach.

Craniopharyngiomas are another primary CNS tumor with molecular subtypes for which targeted treatments are being developed. These are rare suprasellar tumors that occur among children and adults and can cause substantial impairment through compression of critical structures and morbidity of treatments.73 Subtypes are recognized based on single driver mutations and include the 600E BRAF mutation in approximately 95% of papillary craniopharyngiomas (seen predominantly in adults), whereas catenin beta-1 (CTNNB1) mutations were identified in 96% of adenomatous craniopharyngiomas (more common among children).74 The combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib resulted in a rapid objective response and symptom resolution for a young adult with a papillary craniopharyngioma.75 This led to a development of a phase II trial of BRAF/MEK inhibitors (Alliance A071601, NCT03224767) for this patient population. The study includes two separate cohorts and the BRAF/MEK inhibitor combination (vemurafenib/cobimetinib) is administered either in the neoadjuvant setting (cohort A), with the goal being tumor regression to decrease the morbidity of standard-of-care treatment and improve long-term control, or in the recurrent disease (cohort B) setting for which no good treatment options exist.

CONCLUSION

Dramatic advances in our understanding of the molecular biology of tumors have driven a rapid evolution in the taxonomy of CNS tumors, with concomitant improvements in therapeutic decision-making and clinical outcomes. The revised 2016 WHO classification of CNS tumors clearly illustrates the modern paradigm of integrated molecular and histologic diagnoses, provides an effective framework for continued incorporation of molecular findings into pathologic diagnoses, and highlights the importance of surgical sampling not only at initial presentation but also at recurrence to more accurately capture the molecular evolution of these tumors and customize treatment. Future analysis of the increasingly vast amounts of information obtained from genomic sequencing, epigenetic profiling, and proteomic analyses is likely to greatly increase the precision and complexity of tumor diagnoses. Incorporation of this accumulating information in ongoing and future clinical trials is expected to result in better outcomes for patients with primary CNS tumors and lead to personalized treatment options.

References


Over the past few decades, the widespread availability of improved sequencing techniques has contributed immensely to our understanding of the cancer genome and therefore also to our knowledge of clinically actionable mutations in brain tumors. The discovery of a variety of genetic driver mutations in these tumors has enabled us to integrate these findings into the diagnostic process and to implement targeted treatment strategies in affected patients by directing them to appropriate clinical trials. Here we summarize recently discovered driver mutations in low-grade gliomas, glioblastomas (GBMs), craniopharyngiomas, and meningiomas and discuss the diagnostic and therapeutic implications of these findings.

TARGETED TREATMENT OF LOW-GRADe GLIOmAs

On the Involved Tumor Entities

Low-grade gliomas are generally considered World Health Organization (WHO) grade 1 or 2 tumors, but the current WHO classification and its emphasis on molecular characteristics has made the distinction between tumor grades less clear. The revised classification now emphasizes molecular similarities, with only minimal morphologic and subjective differences between grades 2 and 3. This is reflected in the decreased difference in survival between grades 2 and 3 IDH-mutant (IDHmt) astrocytoma, and, taken together, this suggests more of a continuum between grades. Instead, the WHO appropriately now distinguishes between types of IDHmt glioma (astrocytoma for those 1p/19q intact and oligodendroglioma if 1p/19q is codeleted). There is now compelling evidence that patients with grade 2 or 3 IDH wild-type glioma with TERT mutations and polysomy of chromosome 7 plus loss of heterozygosity of chromosome 10q have similar outcomes compared with those with GBM.1,2 In light of this, when considering targeted treatment of gliomas, the focus should not be so much on grade but on the molecular targets.

O-6-Methylguanine-DNA Methyltransferase

Targeted cancer therapies are drugs that block the growth and spread of cancer by interfering with specific molecules that are involved in the growth, progression, and spread of cancer.3 If O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status is considered, alkylating and methylating chemotherapy can be considered targeted treatments. Lomustine and temozolomide are particularly effective in the presence of a methylated MGMT promoter. In most tumors with an IDH mutation, a so-called CpG island hypermethylated phenotype is present; hypermethylation affects the MGMT promoter in 90% to 95% of cases, resulting in decreased expression of MGMT.4 This explains, at least in part, the increased sensitivity of IDH-mutated tumors to these agents compared with GBM in clinical trials of first recurrences. Other mechanisms that are dependent on the function of the normal IDH gene are, however, probably also relevant. IDH mutations increase levels of 2-hydroxyglutarate and decrease levels of α-ketoglutarate, which leads to a number of altered cell processes. The alkB homolog DNA repair enzymes are involved in the repair of methylated DNA lesions, such as 1-methyl adenine and 3-methyl cytosine, and they are α-ketoglutarate...
dependent. Lower \( \alpha \)-ketoglutarate levels in \( IDH \)mt tumors may contribute to decreased DNA repair through AlkB homolog DNA repair.

**PI3K/mTOR Pathway**

The upregulation of this pathway plays a major role in GBM but may also be relevant in lower-grade gliomas. Earlier studies found the prognosis of patients with methylation of the \( PTEN \) promoter region and with expression of phospho-S6 to be worse. Alteration of the receptor tyrosine kinase–RAS-PI3K pathway and deletion of the \( PTEN \) region are frequent events at the time of malignant progression of \( IDH \)mt glioma. Everolimus, an mTOR inhibitor, showed dramatic responses in subependymal giant-cell astrocytomas in patients with tuberous sclerosis, a rare genetic disease characterized by mutations in \( TSC1 \) or \( TSC2 \). An uncontrolled trial explored whether everolimus improved outcomes of recurrent grade 2 glioma. Fifty-eight patients were enrolled, with a variety of prior treatments including surgery only, and codeleted and noncodeleted tumors. The report suggests that the vast majority of patients were still grade 2 at the time of progression, and the reported 6-month progression-free survival was 84%. In the absence of a control arm, definitive conclusions are difficult to reach, as many of these tumors tend to be slow growing and may take quite some time to reach standardized endpoints of progression, even in the absence of treatment. Notably, positivity of phospho-S6 was found to be correlated with methylation of \( PTEN \) and with decreased progression-free survival. Further well-controlled studies are required to demonstrate the clinical activity of mTOR inhibition in this setting.

**Targeting IDH**

The discovery of \( IDH \) mutations as a key driver for a subset of gliomas has drastically altered our understanding of gliomas. The protein that is encoded by the mutant gene loses its normal enzymatic activity and gains the ability to produce an oncometabolite, \( 2 \)-hydroxyglutarate (\( R-2 \)-HG). \( 2 \)-HG induces increased histone and DNA methylation and blocks cellular differentiation. \( R-2 \)-HG competitively inhibits \( \alpha \)-ketoglutarate-dependent enzymes, which play crucial roles in gene regulation and tissue homeostasis. After the discovery of \( IDH \) mutations in glioma, several other tumors types were found to have frequent \( IDH \) mutations, including acute myeloid leukemia, cholangiocarcinoma, and certain sarcomas. Several inhibitors of the altered protein have entered the clinical arena, and responses have been observed in acute myeloid leukemia. However, this was not correlated with the reduction in plasma \( 2 \)-HG and appeared to be due to a differentiation of the tumor cells, but complete molecular responses have also been observed. In glioma, initial results appear less impressive, but a first presentation of the results of AG-120, an oral IDH inhibitor, in unenhancing low-grade glioma suggested that the growth rate of low-grade glioma could be affected. Further confirmatory studies are needed.

In vitro studies have suggested that increased \( 2 \)-HG and decreased \( \alpha \)-ketoglutarate may sensitize tumor cells to radiotherapy and to chemotherapy, which argues against combination strategies of mutated IDH protein inhibitors with either chemotherapy or radiotherapy. However, in vivo studies failed to confirm this, with no interference with the effect of radiotherapy but also no single-agent activity despite a clear reduction of \( 2 \)-HG. These studies also confirmed the low brain penetration of AG-120, which is a major drawback, as many of the relevant tumors are unenhancing. More novel compounds such as AGI-5198 are brain penetrant and may inhibit the products of both \( IDH1 \)- and \( IDH2 \)-mutated genes. This latter compound showed a more pronounced reduction of intratumoral \( 2 \)-HG in an intracranial glioma model. In this model, some single-agent activity was observed, with increased activity in combination with radiotherapy compared with radiotherapy alone but no increased survival with the combination. Also, neither inhibition of the effects of temozolomide nor increased activity was demonstrated. A fundamental question is whether \( IDH \)mt tumors still rely on the \( IDH \) mutation–induced metabolic alterations at later stages of the clinical course or whether other genetic events have taken over. This has important implications for the stages of disease at which these agents could be clinically meaningful. Despite the discovery of \( IDH \) mutations more than a decade ago and the subsequent wealth of information on the pathogenic role of \( IDH \) mutations, clinical progress has been disappointing. Nevertheless, inhibitors of the \( IDH \)mt protein remain a very promising group of agents with potentially huge clinical implications that warrant further study.

Beyond direct inhibition of mutant IDH enzyme, recent data have suggested several approaches for targeted therapy.
specific for IDHmt gliomas. One of the well-described epigenetic effects of IDH mutation is a global increase in CpG methylation across the genome, a phenomenon that has been called CpG island methylator phenotype.\(^7\) In one preclinical study, treatment of IDHmt models with the demethylating agent decitabine resulted in decreased growth rates and increased evidence of differentiation.\(^8\) Another study has shown that DNA hypermethylation induced by mutant IDH also results in a reduction in binding of cohesin and CCCTC binding factor proteins that alter its insulator function and resulted in increased expression of PDGFR\(A\).\(^9\)

Treatment of a gliomasphere model with 5-azacytidine resulted in decreased methylation and increased CCCTC binding factor binding at these sites and related decreased expression of PDGFR\(A\). These observations suggest that the use of demethylating agents, or other epigenetic modifying drugs, may be a reasonable approach for further investigation in clinical trials in these patients. In addition to epigenetic approaches, a recent publication suggested that metabolic targeting of IDHmt tumors may be feasible using nicotinamide phosphoribosyltransferase inhibitors to reduce NAD\(^+\) levels.\(^10\) Unfortunately, no corresponding clinical data are yet available. Thus, the clinical value of these findings still needs to be determined.

**BRAF V600E–Mutated Glial Tumors**

Abnormalities in the BRAF gene resulting in increased signaling through the mitogen-activated protein kinase pathway are characteristic of several subgroups of glioma. In gliomas, the most frequent abnormality in the BRAF signaling pathway is the tandem duplication at 7q34 resulting in a transforming fusion gene between KIAA1549 and BRAF (BRAF duplication or BRAF-KIAA1549 fusion gene), which is frequently present in fossa posterior pilocytic astrocytoma and in non–NF1 optic nerve glioma.\(^11\) BRAF V600E mutations are also of high clinical interest, as these mutations are druggable with high response rates (e.g., in melanoma). BRAF V600E mutations are mutually exclusive with the BRAF-KIAA549 fusion gene and are present in 33% of the non–posterior fossa pilocytic astrocytoma. They are also relatively common in pleomorphic xanthoastrocytoma (43%–66%), anaplastic pleomorphic xanthoastrocytoma (65%), and ganglioglioma (18%–43%), especially if located in the brainstem;\(^13\) they are also found, although infrequently, in adult glioma (GBM, 2%; adult low-grade glioma, 0%–3%).\(^14\) They are also frequent in the novel and rare entity of epithelioid GBM, for which the distinction from anaplastic pleomorphic xanthoastrocytoma is unclear. In children, approximately one-third of BRAF V600E–mutated low-grade gliomas are located in the midline (diencephalon, brainstem),\(^15\) and they have a less favorable prognosis, especially in the presence of CDKN2A mutations. In a recent phase I trial, dabrafenib has shown promising response rates in pediatric patients with relapsed or refractory BRAF V600E high- and low-grade gliomas.\(^16\)

Because BRAF V600E–mutated tumors may be treated with targeted agents, either alone or in combination with a mitogen-activated protein kinase pathway inhibitor to overcome paradoxical mitogen-activated protein kinase pathway activation, the finding of this abnormality has therapeutic implications. Responses in glioma to these agents have been described, at present mostly in case reports. More detailed clinical (umbrella) studies,\(^17,18\) including a clinical trial of the BRAF inhibitor vemurafenib in children with recurrent/refractory BRAF V600E–mutant gliomas (NCT01748149), are ongoing.

In the general glioma population, BRAF V600E mutations are infrequent, but routine testing is indicated in the relevant histologies, which include tumors originating in the medial part of the temporal lobe, brainstem, and mesencephalon. More rare genetic lesions in pilocytic astrocytoma include NF1, KRAS, and RAS mutations and FGFR1 and other BRAF fusions.\(^19\)

First-generation RAF inhibitors (vemurafenib/PLX4720, RAFi) cause paradoxical activation of the mitogen-activated protein kinase pathway in BRAF-fusion tumors, and these tumors are not candidates for first-generation BRAF inhibitors.\(^20\) Newer agents (PLX8394) may overcome this, but clinical data are not yet available.

**NOVEL MOLECULAR TARGETS INCLUDING PARP/IDH/FUSIONS IN Glioblastoma**

**Overview**

Although targeted therapies have had a considerable impact on patient outcomes in many solid tumors, GBM remains an exception. Despite many alterations in specific pathways in various molecular subtypes of GBM, to date targeting of specific mutations or alterations has failed to demonstrate strong activity in these tumors. One possible explanation for this failure is the lack of specific consensus mutations seen in other tumor types (e.g., BRAF V600E in most GBM subtypes).\(^21\) However, recent data point to several potential alterations and subtypes in GBM that may be amenable to targeted therapy, including targeting of DNA repair pathways using PARP inhibitors, targeting the IDH mutant enzyme as well as some of the metabolic and epigenetic effects of these mutations, and targeting various fusion proteins that appear at low frequency but may provide a more biologically relevant target in GBM.

**PARP Inhibitors in IDH Wild-Type and IDHmt Glioblastoma**

Alkylating agents have been a mainstay of treatment of GBM and other gliomas for many years but unfortunately with only moderate overall clinical efficacy as single agents. The most commonly used modern alkylating agent is temozolomide, which is a monofunctional alkylator that methylates DNA at several sites, including N7 guanine, N3 adenine, and O6 guanine. The sensitivity of gliomas to O6 methylation requires intact mismatch repair, and the main resistance mechanism in gliomas for O6 methylation is the expression of the MGMT enzyme, and expression of MGMT is in turn regulated by CPG island methylation of its promoter.\(^22,23\) Resistance to methylation at N7 and N3 sites requires intact base excision repair pathways. PARP activity is necessary...
for efficient base excision repair,36 and PARP inhibitors have been hypothesized to have potential activity in gliomas through this mechanism.37 In addition, PARP inhibitors have been shown to be particularly effective in tumors with defects in homologous recombination of double-stranded DNA breaks, including cancers with BRCA mutations such as breast cancer.38 The potential relevance of defects in the homologous recombination pathway and PARP inhibitors in IDH-mutated gliomas is discussed further below.

Several lines of evidence have suggested potential efficacy of PARP inhibitors in GBM and specific GBM subtypes. Multiple targeted agents that inhibit PARP activity have been developed, and several have developed efficacy and have received U.S. Food and Drug Administration approval in breast and ovarian cancer. These inhibitors typically work by inhibiting the PARylation activity of PARP1 or PARP2 proteins, result in trapping of PARP proteins at locations of DNA damage to varying degree, depending on the specific inhibitor. PARP inhibitors have been demonstrated to reduce resistance to temozolomide in models of GBM and other tumor types.39-42 Other preclinical studies have suggested that loss of PTEN, which is common in GBM, results in synthetic lethality when combined with PARP inhibitors.43 These observations have led to several clinical trials of PARP inhibitors with temozolomide in GBM and other cancers. A randomized phase I/II study of the PARP inhibitor ABT-888 with temozolomide in recurrent GBM has been published,44 with patients randomized between two temozolomide schedules and with 6-month progression-free survival as the primary endpoint. The study showed no benefit of the combination of temozolomide with ABT-888 in terms of progression-free survival and found that a 5-day schedule of temozolomide was much better tolerated in terms of hematologic toxicity with ABT-888 compared with a 21-day schedule. Multiple clinical trials with different PARP inhibitors in GBM are completed or ongoing, including BSI-201 (NCT00687765), olaparib (NCT03212274 and NCT02974621), veliparib (NCT02152982), and BGB-290 (NCT03150862).

**IDH as a Therapeutic Target in Glioblastoma**

As summarized above, mutations in IDH1 and IDH2 genes are a common feature of grade 2 and grade 3 gliomas. IDH mutations are seen less frequently overall in GBM but are seen at high frequencies in the tumors that progress to grade 4 from initial lower grade tumors. These observations again highlight the substantial differences in biology between IDHmt and IDH wild-type gliomas and suggest that the optimal therapeutic approaches are likely to be very different in these groups, regardless of tumor grade.

One therapeutic approach, summarized above, is the use of inhibitors that block the neomorphic activity of the mutant IDH proteins. Additional clinical trials with multiple different IDH inhibitors are ongoing in GBM, several of which are thought to be relatively brain penetrant (NCT02481154, NCT03343197, NCT02273739, NCT02977689, and NCT02381886). However, as stated above, it remains to be determined whether mutant IDH activity is necessary as a maintenance signal in gliomas and if there is a cooperative role of the IDH mutation with later oncogenic events.

As described above, there is abundant evidence from several cancer types that PARP inhibitors are particularly effective, and can be synthetically lethal, in tumors with inherent defects in homologous repair such as those with BRCA mutations. Recent data suggest that gliomas with IDH mutation may harbor a BRCA-like phenotype.45,46 These studies show that IDHmt cells demonstrate defects in homologous repair and an increase in double-stranded breaks compared with IDH wild-type cells, and effects of IDH mutation could be mimicked by addition of 2-HG alone. Furthermore, IDHmt cells showed high sensitivity and synthetic lethality when treated with PARP inhibitors. Both PARP inhibitor sensitivity and homologous repair defects in these cells could be reversed with direct IDH inhibitors, supporting the idea that this phenotype is induced by IDH mutation and 2-HG production and is dependent on persistent neomorphic enzyme activity.46 Treatment with temozolomide in this model also demonstrated enhanced cytotoxicity when combined with PARP inhibitors.45

Last, there is growing data that IDHmt gliomas may represent a potential target for checkpoint inhibitors and other immunotherapeutic approaches. A peptide vaccine targeting mutant IDH protein has demonstrated some activity in preclinical models and is currently in early-phase clinical trials (NCT02454634). Treatment with temozolomide in IDHmt gliomas has also been shown to induce in some patients a hypermutator-like phenotype, which has the potential to produce numerous neoantigens that may sensitize to checkpoint inhibitors48 in a manner analogous to that seen with microsatellite instability.49 The use of checkpoint inhibitors in this hypermutator population is currently being tested as single agent and in combination with radiation (NCT02658279 and NCT02968940), and results are eagerly awaited.

**Gene Fusions as Therapeutic Targets in Glioblastoma**

Chromosomal alterations resulting in expression of functional fusion genes have proved to be important functional drivers and therapeutic targets in multiple cancers (e.g., chronic myeloid leukemia, lung cancer). Given the overall failure of mutation-directed therapies in clinical trials of IDH wild-type GBM, the recent identification of multiple gene fusions that appear to be potential drivers of tumor biology has resulted in the hope that these fusions may turn out to be effective therapeutic targets. One early analysis of RNA sequencing data from GBM samples identified novel intrachromosomal rearrangements that were predicted to result in in-frame fusion proteins of the FGFR3 and TACC1 or TACC3 genes in a small subset (3.1%) of GBM samples analyzed.50 Functional analyses of the FGFR3-TACC proteins demonstrated that they were oncogenic when introduced into astrocytes in vitro and in vivo and caused mitotic abnormalities that resulted in aneuploidy. Treatment of transformed cells with FGFR small-molecule inhibitors resulted in tumor cell growth in vitro and in vivo, suggesting the potential...
therapeutic efficacy of FGFR inhibitors in human GBM tumors driven by this fusion. Additional analyses using combinations of whole-exome, copy-number, and RNA sequencing approaches have identified additional potentially pathogenic fusions in small percentages of high-grade gliomas:

- **EGFR** fusions, including *EGFR-SEPT14* and *HMGA2-EGFR*
- Multiple fusions of *NTRK1*, including *NFASC-NTRK1* and *BREV-NTRK1*
- **ROS1** fusions in GBM
- *PTEN-COL17A1* fusions in GBM
- **MET** fusions in approximately 10% of pediatric GBM
- *PTPRZ1-MET* fusions in anaplastic astrocytoma
- The *KIAA1549:BRAF* fusion, which has been observed frequently in grade 1 pilocytic astrocytoma, has also been reported to occur at low frequency in other pediatric and higher grade gliomas.

Given the rarity of these fusion genes in the general population and the advanced methods needed to identify them, the data on the actual therapeutic efficacy of targeted treatments in tumors harboring specific alterations are sparse. However, one multicancer study estimated that 4.4% of GBM harbor a potentially druggable fusion protein, including those involving ALK-ROS1-RET, FGFR, and NTRK. 

One pediatric patient whose tumor harbored a MET fusion was treated with crizotinib, with reported clinical and radiographic response. The rarity of these fusions in the general GBM population also makes enriched trials challenging, but several FGFR inhibitors and other targeted therapies are currently in clinical trials for GBM or in basket type enriched trials that include GBM.

### PRECISION MEDICINE IN CRANIOPHARYNGIOMAS AND MENINGIOMAS

**Craniopharyngiomas**

Craniopharyngiomas are locally aggressive, low-grade epithelial neoplasms that arise in the suprasellar region of the brain. In general, craniopharyngiomas are relatively uncommon, accounting for about 1% to 3% of all brain tumors in the United States. Nevertheless, these tumors can cause devastating symptoms in affected patients, because they can compress and infiltrate the adjacent anatomic structures, such as the pituitary gland, optic nerves, hypothalamus, and brainstem. On the basis of this anatomic location, tumor growth itself as well as surgery and radiation in this area may cause headaches, visual deficits, panhypopituitarism, cognitive deficits, personality changes, and hypothalamic dysfunction.

Besides these interventional challenges, the clinical management of these patients is often impeded by the lack of standardized clinical practice guidelines and effective systemic therapies.

Craniopharyngiomas can be divided into two histologic subtypes with distinct features. Adamantinomatous craniopharyngiomas (ACPs) can occur in children and adults, whereas papillary craniopharyngiomas (PCPs) occur mainly in adults. However, if only sparse epithelium is present in the sample obtained or in case of small biopsies in general, establishing a final diagnosis exclusively on the basis of histologic features can be challenging.

Using whole-exome sequencing, a recent study identified highly recurrent driver mutations of craniopharyngiomas that can aid distinguishing the two histologic subtypes: activating mutations in the *CTNNB1* gene were found in 95% of all ACPs analyzed, indicating that the WNT pathway plays a crucial role in the tumorigenesis of this craniopharyngioma subtype. Furthermore, whole-exome sequencing revealed that recurrent mutations in *BRAF* V600E were found in 95% of all analyzed PCPs. Of note, the detected alterations in BRAF V600E and *CTNNB1* were found to be clonal and mutually exclusive in each particular tumor subtype, highlighting the importance of these findings for diagnostic purposes as well as for the clinical management of these patients.

With regard to diagnostic tools, immunohistochemistry can now be used to classify suprasellar tumors. In PCPs, beta-catenin is localized in the cell membrane, whereas in ACPs, beta-catenin shifts into the cytoplasm and nucleus and can be found mainly in cell clusters and scattered single cells. Recently, a mutation-specific antibody (VE1) selectively recognizing *BRAF* V600E but not *BRAF* wild-type has been developed, which may help distinguish PCP from ACP. However, it must be kept in mind that this antibody can cross-react with other *BRAF* wild-type tumors, such as endocrine tissues and cilia. In these cases, allele-specific genetic testing can help confirm the suspected diagnosis.

These findings may lead to a paradigm shift with regard to targeted treatment options for patients with craniopharyngioma. To date, agents targeting the WNT-signaling pathway are unfortunately still early in development. In contrast, BRAF inhibitors have already shown promising response rates in patients with *BRAF* V600E–mutant melanomas, gangliogliomas, pleomorphic xanthoastrocytomas, and hairy cell leukemias. Therefore, patients with PCP might benefit from these treatment options and can be enrolled in suitable clinical trials.

Spectacular results have already been achieved in several patients. A recently published case report demonstrated a near complete response to treatment with vemurafenib monotherapy in a patient with PCP, but after interruption of treatment, the tumor showed rapid regrowth within only 6 weeks. After restarting treatment with vemurafenib, tumor growth was stabilized 7 months after initial treatment. Other published cases pursued a combined systemic treatment strategy. A dramatic intracranial response was recently shown in a patient with a *BRAF* V600E–mutant PCP who had previously undergone several urgent neurosurgical resections because of a rapidly growing craniopharyngioma with a large cystic component. Derived from research results in patients with melanoma, to improve the efficacy of treatment and to prevent an early resistance to the *BRAF* inhibitor dabrafenib, the MEK inhibitor trametinib was added.
after 20 days. After 35 days of systemic treatment, the solid component of the PCP was reduced by 85% and the cystic component by 81%. Histologic examination of the tissue collected before and after treatment revealed that the Ki-67 proliferation index of 20% before treatment was reduced to 0.5% after systemic treatment. As a result of the immune response within the tumor, foamy macrophages and CD8-positive T cells were detected in posttreatment samples. Interestingly, circulating BRAF V600E was observed found in the patient’s blood during the treatment course.92

Other case reports have demonstrated similar successful response rates in patients with PCP who were treated with a combination of BRAF and MEK inhibitors.94,95 On the basis of these promising results, a multicenter Alliance for Clinical Trials in Oncology–sponsored phase II clinical trial investigating the role of dual BRAF and MEK inhibition in patients with newly diagnosed as well as recurrent PCP was subsequently initiated and is currently recruiting patients (NCT03224767). In this trial, patients will be treated with vemurafenib and cobimetinib. Furthermore, the investigators plan to analyze PCP tissue before and after treatment with whole-exome and RNA sequencing to identify genetic alterations that may evolve during the period of treatment, which may help further refine therapeutic strategies for affected patients.

Meningiomas

Accounting for more than one-third of brain tumors, meningiomas are the most common primary tumor in adults.96 Most meningiomas (80%) are classified as WHO grade 1 and treated with surgical resection.97 However, this treatment approach can be challenging and is associated with high morbidity in some anatomic locations, including the skull base.98 About 15% to 20% and 1% to 3% are classified as atypical (WHO grade 2) and anaplastic (WHO grade 3) meningiomas, respectively. The management of grades 2 and 3 meningiomas remains difficult. Because not all patients can be successfully treated with surgical resection alone, a combined approach with radiation is frequently pursued in affected patients.99 WHO grade 1 meningioma have reported 5-year recurrence rates up to 20%, but the likelihood for recurrence after 5 years is much higher in WHO grade 2 (up to 40%) and WHO grade 3 (up to 94%) meningiomas.100-102 Compared with WHO grade 1 meningiomas, WHO grades 2 and 3 meningiomas are associated with a significantly higher 5-year mortality rate, ranging from 21% for atypical to 68% for anaplastic meningiomas.103 Although the WHO grading system is a good predictor of recurrence and prognosis of these tumors, it does not hold prognostic value for response to treatment.

Since the 1990s, it has been known that inactivation of the tumor suppressor NF2 by either monosomy 22 or mutations is an established driver in approximately 50% of meningiomas,104-107 but until 2012, little was known about the underlying clinically actionable drivers in those tumors.

Moreover, studies of systemic therapies in recurrent grade 2 and 3 meningiomas in recent years have unfortunately produced only disappointing results. Among a few, the chemotherapy trabectedin, which is routinely used for advanced sarcoma as well as for ovarian cancer,108,109 has shown promising activity in high-grade meningioma in vitro110 and is currently being investigated in a randomized, multicenter phase II trial for patients with recurrent WHO grade 2 and 3 meningiomas (EORTC-1320-BTG).

In 2013, whole-genome and whole-exome sequencing in meningioma tissue samples revealed relatively simple genomes with fewer copy-number alterations, translocations or rearrangements, and mutations than usually observed in other tumors in adult patients. Focal NF2 inactivation was present in more than 40% of cases. In up to 13% and in approximately 5% of tumors lacking NF2 aberrations, AKT1 mutations as part of the PI3K/AKT/mTOR pathway and SMO mutations as part of the Hedgehog pathway, respectively, were present.111,112 Interestingly, more than 60% of meningiomas harboring AKT1 and SMO mutations were found to be originating in the skull base, indicating that targeted agents may potentially facilitate treatment of these patients in the future.111

On the basis of these findings, a phase II trial of the Alliance for Clinical Trials in Oncology is currently analyzing the activity of SMO, AKT1, and FAK inhibitors in recurrent or progressive meningiomas harboring SMO, AKT1, or NF2 mutations (NCT02523014). A variety of other driver mutations in meningiomas have since been described, furthermore suggesting that each individual mutation status correlates with a designated clinical phenotype. In secretory meningiomas, combined mutations of KLF4 K409Q and TRAF7 that were mutually exclusive of NF2 mutations were found in all samples examined.113 TERT promoter mutations were found to be associated with a significantly shorter time to recurrence.114 PIK3CA mutations, also a member of the PI3K/AKT signalling pathway, were found to be as common as AKT1 and SMO mutations in non-NF2-mutant meningiomas, which were located predominantly in the skull base.115 Moreover, in patients with rhabdoid meningiomas, inactivation of the tumor suppressor gene BAP1 is associated with a shorter time to recurrence.116

A recent study examining the immune infiltrate of WHO grades I to III meningiomas suggests that there might also be a role for immunotherapy in these tumors. In this study, PD-L1 expression was found to be increased in anaplastic meningiomas, which caused a substantial decrease of infiltrating T lymphocytes combined with an increase of forkhead box protein P3, expressing immunoregulatory T cells. These mechanisms may contribute to an immunosuppressive microenvironment and therefore to the aggressive phenotype of this tumor subtype.117 As a result, a phase II trial on the role of pembrolizumab in recurrent or residual high-grade meningiomas has just been initiated and is currently recruiting patients (NCT03279692).

CONCLUSION

In summary, the identification of targetable driver mutations in low-grade gliomas, GBMs, craniopharyngiomas, and meningiomas has opened up new potential treatment options
For affected patients. On the basis of these findings, the efficacy of new targeted agents is currently being investigated in clinical trials. However, we must further refine our knowledge of the molecular background of these tumors to effectively treat patients with these tumor entities in the future.

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DEVELOPMENTAL THERAPEUTICS AND TRANSLATIONAL RESEARCH
Patterns of Response and Progression to Immunotherapy

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OVERVIEW

Patterns of response and progression to immunotherapy may differ from those observed with drugs such as chemotherapy and molecularly targeted agents. Specifically, some patients experience a response after progression that is retrospectively named pseudoprogression. This phenomenon of pseudoprogression, first reported in patients with melanoma who were treated with ipilimumab, has led to the development of immune-specific related response criteria, such as irRC (immune-related response criteria), irRECIST (immune-related RECIST), and iRECIST (immunotherapy RECIST) that allow continued treatment beyond progression. However, the rate of pseudoprogression has never exceeded 10% of patients across tumor types. Conversely, rapid progressions after immunotherapy, called hyperprogressions, were reported by three different teams in 9% to 29% of patients treated with immunotherapy. Because of the absence of control arms in these studies, it remains to be determined whether these rapid progressions reflect a detrimental effect of immunotherapy in these patients. Finally, preliminary data suggest that immunotherapy might also affect response to subsequent standard therapies. In total, given the rarity of pseudoprogressions across tumor types and the recent description of hyperprogressions, classic RECIST remains a reasonable and rational method to assess response to immunotherapy. Continuation of treatment beyond progression should be proposed only in carefully selected patients whose clinical conditions have improved and who have not experienced severe toxicities. Although there is an urgent need to identify predictive biomarkers of efficacy to immunotherapy, there is an equally urgent need to identify predictive factors of progression or possibly hyperprogression.

Immune evasion, now established as a fundamental hallmark of cancer, has long been an area of research and interest for the development of novel therapeutics in oncology, as illustrated by the use of intracavitary bacillus Calmette-Guérin in the treatment of superficial bladder tumors to stimulate immune response since the 1970s.1,2 The immune system is able to recognize antigens derived from cancer cells and therefore distinguishes cancer cells from their normal counterparts to generate a tumor-specific T-cell immune response against the tumor.3 Immune checkpoints are receptors expressed on peripheral tissues and immune cells and are involved with the maintenance of self-tolerance and modulation of the immune response (as a physiologic negative feedback loop) to prevent autoimmune reactions. Cancer cells can escape tumor-specific T-cell responses via engagement of inhibitory immune checkpoints (coinhibitory signals), which thus induces immune tolerance and tumor progression.3 Several strategies have been developed to stimulate cancer-specific immune response, including vaccines, cytokines, immune checkpoints inhibitors, and adaptive T-cell therapies using transfer of genetically engineered T cells that specifically target tumor antigens, such as chimeric antigen receptor (CAR) T cells.

Ipilimumab targets CTLA-4 expressed on T cells and downregulates T-cell activation.3 It was the first immune checkpoint inhibitor to be approved by the U.S. Food and Drug Administration. PD-1 is another checkpoint that inactivates T cells by binding to its ligand PD-L1, which is expressed in peripheral tissues and cancer cells. Several anti–PD-1 and anti–PD-L1 antibodies have been developed in the clinic.3,4 Immune checkpoint inhibitors represent a major breakthrough in oncology, because they have been shown to improve survival across a broad range of tumor types.5-13 However, the majority of patients with cancer do not benefit from these drugs.14

The main goal of any medical intervention in oncology is to improve quality of life and/or overall survival. To expedite drug development, surrogate endpoints are used to assess the efficacy of new drugs and mostly include endpoints that are based on the evaluation of tumor shrinkage or increase with time. RECIST are the most commonly used response assessment criteria in clinical research.15 These criteria have been developed in the era of chemotherapy, for which efficacy
usually correlates with tumor shrinkage. Limitations of these criteria have been identified with the emergence of molecularly targeted agents that sometimes improve overall survival without any tumor shrinkage, such as imatinib for the treatment of gastrointestinal stromal tumors or sorafenib for the treatment of hepatocellular carcinoma. Specific criteria, such as the Choi criteria, have been developed to overcome this limitation.

Here, we aim to review the patterns of response and progression to immunotherapy, especially to immune checkpoint inhibitors. Firstly, we describe the radiographic criteria used to assess response to immunotherapy. We then discuss the rationale for treatment beyond progression and its clinical implications. Finally, we challenge the newly reported concept of hyperprogression after immunotherapy.

**ASSESSMENT OF RESPONSE TO IMMUNOTHERAPY BY RADIOGRAPHIC CRITERIA**

**Background**

The evaluation and understanding of antitumor responses in the era of immuno-oncology is becoming increasingly important with the rapid expansion of indications and approvals of checkpoint inhibitors. The response evaluation of immuno-oncology agents requires differentiation from traditional cytotoxic and other molecularly targeted agents. The mechanism of action of immuno-oncology agents is to increase the immune response against the tumor cells, which is accomplished by overcoming the tumor’s intrinsic immune-evasion mechanisms. To date, most response evaluation to immuno-oncology therapy has been performed using RECIST version 1.1 (RECIST1.1), but the need for more precise criteria that are compatible with the observed patterns of responses and the mode of action of immunoncology agents is well documented within the field.

**Classic Response Criteria**

The earliest attempts to standardize response evaluation and thus the efficacy of therapy were in 1981, with the establishment of the WHO criteria. This used bidimensional measurements to determine the total tumor size and, on inception, was widely used; soon, however, there were setbacks that led to changes resulting in the development of RECIST1.0 in the late 1990s. This model used unidimensional rather than bidimensional measurements. On the basis of a meta-analysis of eight studies that included 569 patients, it was concluded that unidimensional measurement of a tumor’s maximum diameter could be sufficient to assess objective response. CT evaluation was determined to be the most reliable and practical method, and similar imaging was required at follow-up to avoid discrepancy in evaluation of responses. As expected, the shortcomings of RECIST1.0 became apparent with time—specifically its applicability to phase III trials in which the progression-free survival and/or overall survival, not overall response rate, was the endpoint. Also, the use of MRI and PET/CT has increased with time, and the incorporation of these newer technologies to assess response has become a challenge. The other important pitfall to RECIST1.0 is that the assessment of lymph nodes was not included. These shortcomings led to the development of RECIST1.1. Important changes included the number of lesions to be assessed (decreased from a maximum of 10 to five in total), a change in the number of lesions allowed per organ (from five to two), and the inclusion of pathologic lymph nodes (short axis of 15 mm) as measurable disease. The use of an FDG-PET scan was specifically mentioned for the detection of new lesions. The recommended duration for repeat imaging studies was 6 to 8 weeks.

With the advent of immunotherapy, the use of RECIST in clinical trials resulted in premature discontinuation of therapy in patients with clinical benefit or a later response. This insufficiency resulted in the need for irRC.

**Immune-specific related response criteria.** To estimate the responses of immunotherapy accurately, new criteria called irRC were developed (Table 1). The irRC were established on the basis of data from trials of ipilimumab in patients with advanced melanoma. A delayed but durable clinical response was observed in a subset of patients and was associated with prolonged survival. The new criteria incorporated several key features that allowed patients with atypical responses to continue therapy and without the false label of disease progression; these features included the need for confirmation of progression after it was first documented and the allowance of new metastases. In detail, the irRC consisted of immune-related complete response (irCR; complete disappearance of all lesions), immune-related partial response (irPR; reduction of greater than or equal to 50% in disease burden), immune-related stable disease (irSD; neither irCR nor irPR criteria met), and, last, immune-related...
progression of disease (irPD; an increase in tumor burden by 25% or greater relative to nadir). Four weeks from the first documented response, a repeat imaging is done for confirmation. The overall response rate in the ipilimumab trials was only 10%, but the 2-year overall survival in patients with metastatic melanoma with the use of new criteria of immune-responses was approximately 25%. Although the irRC developed from the experience with advanced melanoma, it was easily translated to other malignancies. Recently, it was shown that patients treated beyond RECIST progression but not progression by irRC had better survival than patients who experienced progression per both criteria, which suggests that irRC use could prevent premature termination of treatment in 14% of patients treated beyond initial RECIST progression without irRC progression. The irRC also have been used to assess response in patients with advanced non–small cell lung cancer (NSCLC) treated with pembrolizumab. The nomenclature of classic endpoints with the irRC includes immune-related overall response rate, the immune-related disease control rate, and the immune-related progression-free survival; these correlate with overall survival. Furthermore, the irRC have been incorporated into the U.S. Food and Drug Administration and European Medicines Agency guidance documents. As expected, the disadvantage of the irRC was realized later. The irRC uses bidimensional measurement (similar to WHO criteria), whereas most of the initial immunotherapy trials used unidimensional measurements per RECIST criteria. Multiple studies demonstrated that bidimensional measurements were subject to variability in responses compared with unidimensional measurements.

To refine the radiologic criteria to assess responses to immuno-oncology therapy even more, the immune-related RECIST (irRECIST) were introduced (Table 1). These criteria combine the criteria of both irRC and RECIST by using unidimensional measurements and require confirmation of progression. In irRECIST, measurable disease is defined as non-nodal metastases of 10 mm or more in the long axis and nodal lesions of 15 mm or more in the short axis. The total tumor burden is the sum of the target non-nodal lesions in the long axis and the target nodal lesions in the short axis dimensions. Similar measurements are used for new lesions. The responses in irRECIST are defined as complete response if there is disappearance of all the target and nontarget lesions if the nodal lesions are less than 10 mm in the short axis. A partial response is a 30% or greater decrease in the tumor burden compared with the baseline and no unequivocal progression in the nontarget lesions. Stable disease, like other response criteria, is neither a complete nor partial response. An increase of 20% or more in the total measurable tumor burden from nadir, with a minimum of 5 mm of progression of nontarget lesions, or the appearance of a new lesion, is considered irPD. An important aspect of these irRC is that the irPD must be confirmed with a repeat assessment at least 4 weeks later to give immunotherapy time to declare a response. If the repeat assessment has new unequivocal progression from the prior imaging studies, or has the appearance of another new lesion, progressive disease is confirmed. Despite these new immune criteria (irRC and irRECIST), many immunotherapy trials since 2010 have used the traditional RECIST criteria, which therefore makes a universal comparison of data from different trials difficult.

In March 2017, a consensus guideline named immunotherapy RECIST (iRECIST) was published after extensive work carried out by the RECIST working group along with the immunotherapy subcommittees (Table 1). The working group planned to create a warehouse of data from immunotherapy trials to validate RECIST1.1. However, during the data review, a wide discrepancy was noted between the trials run by different organizations, including cooperative and industry groups, that had the potential to make the pooled data

### TABLE 1. Immune-Specific Related Response Criteria

<table>
<thead>
<tr>
<th>Measurement Modality</th>
<th>irRC: Bidimensional (Longest Diameter × Longest Perpendicular Diameter)</th>
<th>irRECIST: Unidimensional (Longest Diameter)</th>
<th>iRECIST: Unidimensional (Longest Diameter)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline lesion size, mm</td>
<td>5 × 5</td>
<td>≥ 10</td>
<td>≥ 10</td>
</tr>
<tr>
<td>Minimum no. of lesions to be measured for assessment</td>
<td>10 lesions in total; 5 per organ</td>
<td>5 lesions in total; 2 per organ</td>
<td>5 lesions in total; 2 per organ</td>
</tr>
<tr>
<td>Appearance of new lesions</td>
<td>Incorporated in the sum of the measurements</td>
<td>Incorporated in the sum of the measurements</td>
<td>iUPD; becomes iCPD if PD is eventually confirmed</td>
</tr>
<tr>
<td>CR</td>
<td>Disappearance of all lesions</td>
<td>Disappearance of all lesions</td>
<td>Disappearance of all lesions</td>
</tr>
<tr>
<td>PR</td>
<td>≥ 50% decrease from baseline</td>
<td>≥ 30% decrease from baseline</td>
<td>≥ 30% decrease from baseline</td>
</tr>
<tr>
<td>SD</td>
<td>Neither CR nor PD is met</td>
<td>Neither CR nor PD is met</td>
<td>Neither CR nor PD is met</td>
</tr>
<tr>
<td>PD</td>
<td>≥ 25% increase in the nadir of the sum of target lesions</td>
<td>≥ 20% increase in the nadir of the sum of target lesions with a minimum of 5 mm</td>
<td>≥ 20% increase in the nadir of the sum of target lesions with a minimum of 5 mm</td>
</tr>
<tr>
<td>Confirmation of PD</td>
<td>Yes</td>
<td>Yes, at least 4 weeks after, and up to 12 weeks</td>
<td>Yes, at least 4 weeks after, and up to 8 weeks</td>
</tr>
</tbody>
</table>

Abbreviations: irRC, immune-related response criteria; iRECIST, immune-related RECIST; iUPD, immune unconfirmed progressive disease; iCPD, immune confirmed progressive disease; PD, progressive disease; CR, complete response; PR, partial response; SD, stable disease.
from all the trials difficult to interpret. It was also noted that RECIST1.1 was used to assess primary and secondary endpoints and that irRC and irRECIST had been used for exploratory endpoints to date (often as a comparator to RECIST1.1 within the trial). Because of these discrepancies, the working group with the subcommittees came up with a modified RECIST1.1 for immuno-oncology and named it iRECIST. The hope was that, with the introduction of these guidelines, there would be no variability in the interpretation and analysis of various trials involving immunotherapy.

The definitions from RECIST1.1 formed the basis of the iRECIST criteria, so the definitions of measurable and nonmeasurable disease, as well as target and nontarget lesions, are unchanged. The working group recommended use of a new standard terminology: immune complete response (iCR), immune stable disease (iSD), immune partial response (iPR), and immune unconfirmed progressive disease (iUPD) or immune confirmed PD (iCPD). The main difference between iUPD and iCPD is that iUPD uses the same definition as RECIST1.1 for progressive disease, but iUPD must be confirmed to be considered true progression (iCPD); also a repeat scan must be performed at least 4 weeks, but not more than 8 weeks, after iUPD. The response is considered iCPD when there is an increase of at least 5 mm total of measurements of target lesions from iUPD. A disease can be named iUPD multiple times in a patient on one therapy until there is an iCPD. Unlike RECIST1.1, the response can be categorized as iCR, iPR, or iSD during the follow-up assessment after iUPD, but not after iCPD is reached. For nontarget lesions, the same criteria are followed, and iUPD can be assigned several times; however, a new label—noniCPD/noniUPD—is used when neither iCR nor progressive disease have been reached. The concept of new lesion assessment is noteworthy in iRECIST. Any new lesion should be identified as measurable or nonmeasurable along the same lines of RECIST1.1. If a new lesion is identified (thus meeting the criteria for iUPD) and the patient is considered asymptomatic or stable, then the treatment should not be withheld. Five lesions (no more than two per organ) should be measured and recorded as a new target lesion, and these should not be included in the sum of measures of the baseline target lesions. iCPD in new lesions is defined as confirmation in subsequent scans, or as an increase in the sum of measures in new target lesions of 5 mm or greater, or as any increase in a nontarget lesion that was initially categorized as iUPD.

The best response recorded for the iRECIST criteria is the immune best overall response. After iUPD, in the subsequent reassessment imaging studies, iPR, iSD, iCR, or unequivocal progression in nontarget lesions only can contribute to the immune best overall response unless iCPD criteria are met. These guidelines are recommendations for immuno-oncology clinical trials, especially phase III trials, to encourage the use of both RECIST1.1 and iRECIST. They also recommend that primary outcomes such as progression-free survival, overall survival, and best response should be based on RECIST1.1, whereas exploratory analyses should use iRECIST. Early-phase clinical trials may consider using just iRECIST. During drafting any clinical trial protocol, these guidelines recommend clear mention of specific criteria used for both primary and exploratory endpoints. The final iRECIST guidelines and information about the best way to incorporate these criteria in the design of upcoming clinical trials are available on the European Organisation for Research and Treatment of Cancer public website (www.eortc.org/?s=iRECIST).

It is important to recognize that the treatment responses for immunotherapy differ from those of conventional chemotherapy. The application of the immune-related response criteria is prudent so that premature termination of therapy is avoided. To date, numerous clinical trials in immuno-oncology are underway, and the adoption of iRECIST criteria will ensure a uniform approach to the conduct, interpretation, and analysis of trials.

Rationale for Treatment Beyond Progression and Clinical Implications

Rationale for Treatment Beyond Progression

A progression according to RECIST followed by response is commonly named a pseudoprogression. Pseudoprogressions were first described in patients with advanced melanoma treated with ipilimumab, and later with the anti–PD-1 inhibitors nivolumab or pembrolizumab, and provide the rationale for treating patients beyond progression. The main limitation of RECIST is the assessment of progressive disease that might lead to a premature cessation of an effective immuno-oncology agent that would have induced a pseudoprogression.

Biologic hypotheses might explain the phenomenon of pseudoprogression observed in patients treated with immuno-oncology agents. These agents initially induce the recruitment of activated T cells to the tumor site before they have any antitumor activity, which lead to an artificial increase in tumor size. Inflammatory reactions have been observed in tumor biopsies taken at initial tumor progressions (that eventually were considered pseudoprogressions) of melanoma in patients treated with ipilimumab.

The occurrence of pseudoprogressions was confirmed in larger trials in which treatment beyond progression was allowed. Pseudoprogressions were reported in various tumor types (Table 2), but rates never exceeded 10% of patients treated with immuno-oncology agents. When the rates of pseudoprogressions are calculated, use of all patients who started immuno-oncology agents, and not only the subgroup of patients who continued on treatment after progression, as the denominator is essential. Patients who do not continue immunotherapy after progression usually are patients whose clinical conditions deteriorated and who likely would have no longer benefited from immunotherapy. In most trials with immuno-oncology agents, treatment beyond progression is only allowed in patients whose clinical conditions do not deteriorate.

The identification of baseline characteristics and patients who will most benefit from treatment with immuno-oncology agents beyond progression remains an important challenge.
in the management of solid tumors in the era of immunotherapy. It is critical to avoid premature cessation of a potentially effective agent and, at the same time, to avoid delaying the start of a subsequent potentially effective drug. Indeed, some patients can experience progression rapidly with an immuno-oncology agent, and rapid clinical deterioration makes the patient unable to receive a subsequent, potentially active treatment. A tumor biopsy at the time of disease progression may help evaluate the presence of tumor immune infiltration versus the absence of immune cells in exploratory studies, but this has not yet been proven as a validated biomarker. No reliable assessment has been reported to date to help clinicians decide between a potential pseudoprogression or a real progression, although circulating tumor DNA, if present at baseline, has been shown to decrease in the presence of pseudoprogression.\textsuperscript{62}

### TABLE 2. Rates of Pseudoprogression in Patients Receiving PD-1/PD-L1 Inhibitors in Selected Phase II/III Clinical Trials

<table>
<thead>
<tr>
<th>Study Drug and Reference</th>
<th>Rate of Pseudoprogression, %</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{48}</td>
<td>8.1</td>
<td>17 of 210 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{52}</td>
<td>8.3</td>
<td>10 of 120 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td>Pooled retrospective study of two multicenter, phase III trials to evaluate anti–PD-1 antibodies\textsuperscript{50}</td>
<td>4.6</td>
<td>24 of 526 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td><strong>Non–small cell lung cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{53}</td>
<td>3.4</td>
<td>4 of 117 patients had a tumor burden reduction or no additional progression for at least two tumor assessments after initial RECIST-defined PD</td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{54}</td>
<td>5.5</td>
<td>16 of 292 patients with either (1) appearance of a new lesion followed by a decrease from baseline of at least 10% in sum of target lesions; (2) initial increase from nadir ≥ 20% in the sum of target lesions followed by a reduction from baseline of at least 30%; or (3) initial increase from nadir ≥ 20% in sum of target lesions or appearance of new lesions followed by at least two tumor assessments that showed no additional progression, defined as ≥ 10% additional increase in the sum of target lesions and new lesions</td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{54}</td>
<td>6.9</td>
<td>9 of 131 patients with either (1) appearance of a new lesion followed by a decrease from baseline of at least 10% in the sum of target lesions; (2) an initial increase from nadir ≥ 20% in the sum of target lesions followed by a reduction from baseline of at least 30%; or (3) an initial increase from nadir ≥ 20% in the sum of target lesions followed by at least two tumor assessments that showed no additional progression defined as ≥ 10% additional increase in the sum of target lesions and new lesions</td>
</tr>
<tr>
<td>Pooled retrospective study of three multicenter, open-label trials to evaluate anti–PD-1 antibody\textsuperscript{55}</td>
<td>1.9</td>
<td>10 of 535 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td>Atezolizumab\textsuperscript{56}</td>
<td>3.6</td>
<td>12 of 332 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td><strong>Head and neck squamous cell carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{57}</td>
<td>1.3</td>
<td>3 of 240 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td><strong>Renal cell carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{58}</td>
<td>7.1</td>
<td>12 of 168 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td>Nivolumab\textsuperscript{59}</td>
<td>4.9</td>
<td>20 of 406 patients experienced a PR according to RECIST after a PD</td>
</tr>
<tr>
<td><strong>Urothelial carcinoma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab\textsuperscript{60}</td>
<td>1.6</td>
<td>5 of 310 patients experienced a PR according to RECIST after a PD</td>
</tr>
</tbody>
</table>

Abbreviations: PR, partial response; PD, progressive disease.
Given the rarity of pseudoprogresison and the absence of validated predictors, continued immunoo-oncology treatment beyond RECIST1.1-defined progression should be proposed only for patients who do not experience severe toxicity from these agents and whose clinical conditions have improved (or stabilized in those with rapid progression) with treatment. Additional studies are warranted to identify predictive factors of response to immunoo-oncology agents to guide therapeutic decisions.

Strategies for Treatment After Immunotherapy
Despite impressive results in many different types of tumors in advanced settings, only a small proportion of patients clearly benefit from immunoo-oncology agents. Some patients will eventually develop secondary resistance.

Currently, the main strategy to improve the efficacy of immunotherapy focuses on the development of combination strategies of already-marketed immunoo-oncology agents with other immunoo-oncology agents, but also with molecularly targeted agents, radiotherapy, and chemotherapy, mainly in patients who were not previously exposed to immunoo-oncology agents. Limited data exist on the best strategies in patients who have already experienced progression during immunotherapy.

Data from patients with advanced melanoma showed that BRAF inhibitors induced a brisk and strong CD8+ T-cell infiltrate in human melanoma tissue early during therapy. Preclinical studies have suggested that chemotherapy administered after immunotherapy might improve the balance between immunosuppressive cells and stimulation of immune cells by increasing recruitment of CD8+ T-cells into the tumor microenvironment. In an in vivo model of PD-1 knockout mice, paclitaxel enhanced the expression of major histocompatibility complex class I on cancer cells, which thus increased the recruitment of CD8+ cells. In another in vivo model, delivery of chemotherapy after an immunogenic treatment increased its antitumor activity via an increase in the number of antigen-specific CD8+ T-cells within the tumor microenvironment.

Retrospective studies showed that patients with NSCLC who received salvage chemotherapy (mostly single agents) after immunotherapy achieved a higher overall response rate compared with historical data. As an example, the overall response rate to single-agent chemotherapy after exposure to immunotherapy was 53% in patients with NSCLC compared with 35% in patients whose last chemotherapy was administered before the immunono-oncology agent. A major response to a combination of dacarbazine and cisplatin was reported in a patient with metastatic BRAF-mutated melanoma who had experienced disease failure after treatment with a BRAF inhibitor combination, ipilimumab and nivolumab, despite generally poor efficacy of dacarbazine and cisplatin in patients with this disease.

These preliminary results must be confirmed in larger studies. The adequate sequence of treatment with immunono-oncology agents and other therapies must be explored more, because there are no clear guidelines for patients who have experienced progression with immunotherapy. Better understanding of the tumor immune infiltrate along with factors that will contribute to maintaining an efficient antitumor immune response is key to improve treatment strategies with immunotherapy. One of the most useful, but challenging, methods is to collect tumor samples and blood before starting immunotherapy, during treatment, and at disease progression.

HYPERPROGRESSION: MYTH OR REALITY
Definition of Hyperprogression and Literature Review
With increasing knowledge about immunotherapy, some reports have described rapid progression in patients who start immunotherapy. The main question is whether this rapid progression represents the natural history of cancer growth or is immunotherapy-induced acceleration of tumor growth.

One concept purported to support the phenomenon of immunotherapy-induced hyperprogression comes from randomized trials that compared immunotherapy with chemotherapy in which the overall survival curves clearly favor the chemotherapy arm in the first few months. This has been reported, for example, with nivolumab in head and neck squamous cell carcinoma and in NSCLC in the CheckMate 141 and 057 trials. The fact that the survival curve of the control arm is greater than that of the immunotherapy arm in the first months indicates that a proportion of patients experience worsened disease with immunotherapy compared with chemotherapy. However, it might also only mean that immunotherapy has no activity at all in these patients compared with some activity from chemotherapy.

Three recently published studies have examined the concept of hyperprogression (Fig. 1). In one study, the authors compared tumor growth kinetics in terms of volume before starting immunotherapy and during immunotherapy in patients with various tumor types included in phase I clinical trials. Hyperprogression was defined as a twofold or greater increase in the tumor growth rate in terms of volume during immunotherapy. Hyperprogression was reported in 12 (9%) of 131 patients. The median tumor growth rate ratio was 20.7 (range, 2 to 141). Hyperprogression correlated with worse overall survival.

In a second study, hyperprogression was defined as a time to treatment failure of less than 2 months or a greater than 50% increase in tumor burden in two diameters according to irRC compared with pre-immunotherapy imaging that was obtained within 2 months of the initiation of the immuno-oncology agent, or a greater than twofold increase in progression pace with one diameter. Six (4%) of 155 patients experienced hyperprogression according to this definition.

In the third study, the authors focused on patients with head and neck squamous cell cancer who were treated with PD-1/PD-L1 inhibitors and compared tumor growth kinetics with one diameter before and during immunotherapy. Hyperprogression was defined as a twofold or greater increase in...
in the tumor growth rate in one diameter on immunotherapy. Ten (29%) of 34 patients experienced hyperprogression, and hyperprogression correlated with poor progression-free survival.

Predicting Hyperprogression
Although it is essential to identify predictive biomarkers of efficacy of immuno-oncology agents, it seems even more important to identify predictive biomarkers for rapid progression. Hyperprogression was associated with older age, with a recurrence in an irradiated field in patients with head and neck squamous cell cancer, and with MDM2 amplification. Recently, chromosomal instability identified with next-generation sequencing on cell-free DNA was evaluated in patients receiving immunotherapy and in a control group of patients. The authors were able to accurately predict progression on the basis of chromosomal instability quantification in plasma cell-free DNA: 90% of patients with progression did not have a substantial decrease in the chromosomal number instability score. Interestingly, in five of the six patients who experienced hyperprogression, progression was predicted early with the chromosomal number instability score.

Practical Considerations
The concept of hyperprogression remains controversial, because none of the studies described here had a control arm. Therefore, nobody could predict whether similar tumor growth kinetics would occur in patients without any treatment. No randomized trial to compare immunotherapy with no treatment has been published to date, and only worse overall survival with immuno-oncology agents versus no drug therapy would be a valid demonstration of the hyperprogression phenomenon. However, some patients do experience rapid progression with immunotherapy, and it would be helpful to compare in a quantitative way (and not only a qualitative way with dichotomic criteria such as RECIST) the patterns of progression in trials of immunotherapy compared with chemotherapy.

In any case, we strongly recommend interruption of immunotherapy if rapid progression or hyperprogression is clinically suspected. The disease should be reassessed clinically, and imaging should be performed. This might allow patients to switch to another treatment if the clinical condition is compatible. These findings reinforce the need for caution about the decision to continue an immuno-oncology agent beyond progression, because most progressions are real progressions and not pseudoprogressions.

CONCLUSION
Patterns of response and progression of immuno-oncology agents differ from those seen with chemotherapeutic agents, especially for the assessment of disease progression. Management of disease in patients who experience a response to immunotherapy according to RECIST is similar to the management in those treated with chemotherapy or molecularly targeted agents, although the question of whether immunotherapy could be ceased in long-term responders must be resolved. Similarly, treatment should be continued in patients who experience disease stabilization according to RECIST.
to RECIST. The big challenge is the assessment of disease progression, which has led to the development of irRC. Overall, it is important to keep in mind that pseudoprogressions are the exception rather than the rule. Therefore, treatment beyond progression as proposed in new immune-related criteria should be carried out only in carefully selected patients whose clinical conditions have improved (or stabilized, in cases of rapid progression) with immunotherapy and who have not experienced severe toxicities. Treatment also may be stopped early where there is rapid progression or when hyperprogression is suspected so that the patient can switch to another treatment in a timely manner. This is all the more important given that preliminary data suggests that some patients may have greater responses to subsequent therapies, such as chemotherapy. We believe that classic RECIST are still practical, efficient, and relevant criteria to assess the response and progression to immunotherapy in the vast majority of patients. Although there is an urgent need to identify predictive factors of response to immunoncology agents, it seems equally important to identify predictive biomarkers of progression or possible hyperprogression.

**References**


OVERVIEW

The approvals of six checkpoint inhibitory antibodies since 2011 have established immunotherapy for cancer as a fifth treatment modality after chemotherapy, surgery, radiation, and targeted therapy. Long-lasting responses have been observed in melanoma, non–small cell lung cancer, renal cell cancer, and head and neck cancer, to name a few, and more approvals for these drugs undoubtedly are coming in the near future. The application of checkpoint inhibitors has expanded well beyond melanoma, and, with wider use, the management of the immune-related adverse events (irAEs) that accompany these drugs has received increased attention. In this work, several patient cases are presented that highlight how to optimally manage these unique toxicities and that illustrate the basic principles of care for patients who receive checkpoint inhibition.

Education of the care team and patients and good communication between them are the keys to successful management of irAEs. A recent review comprehensively summarized the important questions that clinicians address when their patients experience irAEs from checkpoint protein inhibition (CPI).¹ The mechanism-based toxicities that constitute irAEs result from potent stimulation of immune responses directed against normal tissues in a scenario in which there is a clinically significant disinhibition or reinvigoration of antitumor immunity.² Data suggest that these adverse effects may be T-cell mediated and that auto-antibodies may cause some of the toxicity.³ Virtually any organ can be affected, and some of the irAEs appear to mimic known autoimmune diseases, yet there are crucial differences between the acute onset and resolution of irAEs and symptoms of classic autoimmune diseases that are often chronic and may be lifelong. The majority of irAEs affect the gut, liver, skin, and endocrine organs.⁴,⁵ However, less common irAEs affect the kidneys, lungs, bone marrow, heart, and nervous system.⁶⁻⁹ The kinetics of onset and resolution of irAEs are well established, and, other than the endocrinopathies, virtually all irAEs will resolve completely with the use of immune suppressants like corticosteroids, infliximab, and mycophenolic acid. The irAEs that occur with combination checkpoint inhibition may occur earlier and last longer than with PD-1/PD-L1 blockade alone. Most irAEs will occur within the first 12 to 24 weeks of treatment, but certain irAEs, including arthralgias and myalgias, may occur with more chronic use of CPI.¹⁰ Uncommonly, irAEs may present at any time during treatment with checkpoint blockade, even years after initiation of therapy, and may even occur after CPI is stopped. For both CTLA-4 and PD-1/PD-L1 blockade, skin irAEs occur first, followed by gastrointestinal, then liver, and finally endocrine adverse effects.⁴,⁵ The exact etiology of irAEs and the mechanisms that distinguish them from the antitumor impact of CPI remain unclear, and it is unknown whether one might dissociate the impact of one from the other. There are some data that select irAEs may be associated with a more favorable clinical outcome with treatment using PD-1 blockade or combination CTLA-4 and PD-1 blockade.¹¹,¹² Patients with melanoma who received nivolumab or pembrolizumab and developed rash or vitiligo had better outcomes than those who did not, and patients who received combination immunotherapy and had gastrointestinal adverse events also had a longer survival than those who did not.¹³ Surprisingly, even when irAEs are treated with corticosteroids or other immune suppressants, no data suggest that clinical outcome is compromised.¹⁴,¹⁵

The use of corticosteroids is the mainstay of management of CPI-induced irAEs. Doses of oral prednisone should range from 1 mg/kg to 2 mg/kg daily for grade 3 or 4 irAEs, and tapering courses of corticosteroids should be given for a minimum duration of 1 month. Patients admitted to the hospital because of complications of irAEs should be treated with intravenous corticosteroids. If symptoms of irAEs do not abate within 72 to 96 hours of corticosteroid initiation, alternative immune suppressants, including infliximab and mycophenolic acid, should be considered. Not uncommonly, a flare of irAE symptoms may be seen as steroids are tapered. With colitis or pneumonitis, a bolus of intravenous methylprednisolone may be given, and the steroid dose should be increased to 1.5 to 2 mg/kg of prednisone or its
accompanied by cramping and abdominal pain. That evening, the patient noted eight episodes of diarrhea in 24 hours. Diarrhea, medicines such as loperamide can be useful to the steroid regimen to avoid gastritis. For grade 1 and additional dose may be administered. Infliximab should not be used for hepatitis, and alternative immune suppressants such as mycophenolic acid should be given. If 6 weeks or more of oral corticosteroids are required to manage irAEs, prophylaxis should be considered for Pneumocystis carinii infection. Proton-pump inhibitor therapy should be added to the steroid regimen to avoid gastritis. For grade 1 and diarrhea, medicines such as loperamide can be useful to diminish the symptoms. Stool samples in patients having diarrhea due to an irAE should also be tested for common gastrointestinal pathogens including Clostridium difficile, as well as bacteria, fungal, ova, and parasites.

Important questions often faced by oncology practitioners are illustrated in the following patient cases. These include when to add an additional immune suppressant if corticosteroids alone do not suffice; whether one may be able to re-treat a patient who had a prior dose-limiting irAE with CPI; and whether patients with existing autoimmune disease should be treated at all with CPI.

**CASE 1: COLITIS IN A PATIENT RECEIVING PEMBROLIZUMAB**

A 65-year-old man with a history of stage III melanoma resected from the right axilla with an unknown primary was diagnosed with metastatic disease after a routine surveillance CT scan showed multiple pulmonary nodules. A needle biopsy of a 2-cm right lung lesion was positive for melanoma, BRAF wild type. He was asymptomatic, and his lactate dehydrogenase level was normal. The patient had a history of an early-stage prostate cancer treated with surgery 18 months ago and was not eligible for any trial. He started treatment with single-agent pembrolizumab therapy; after four doses given every 3 weeks, CT scans for re-evaluation at week 12 showed a near-complete resolution of all lung nodules. He received his fifth dose of the drug at week 13 and noted diarrhea two to three times a day 1 week later, but he did not report this to the care team. The diarrhea abated after 3 days, but 2 weeks after the fifth dose of pembrolizumab, the patient noted eight episodes of diarrhea in 24 hours accompanied by cramping and abdominal pain. That evening, his appetite was poor and he drank very little. He delayed calling the care team until the next morning and was asked to come to the clinic for an evaluation. At that time, he had a blood pressure level of 96/50 mmHg, was tachycardic with a heart rate of 122 beats per minute, and had a mildly tender abdomen. Rectal examination showed minimal stool that was heme negative; the blood urea nitrogen level was 37 mmol/L with a creatinine level of 1.5 μmol/L, and he was admitted to the hospital. The CT scan on admission showed stranding and thickening of the descending and sigmoid colon, without free air seen. Clostridium difficile titers were negative. Intravenous fluid was given, and intravenous methylprednisolone was administered at a dose of 125 mg that afternoon and evening. The diarrhea episodes decreased to four times in the ensuing 24 hours. The next day, the patient felt better and started to eat; he received 120 mg of prednisone. However, he still had four episodes of diarrhea on the second day in the hospital, and he had six diarrheal bowel movements with minimal blood on the third day. The gastrointestinal consultant performed a sigmoidoscopy that afternoon, which showed diffuse ulceration and erythema. A dose of 5 mg/kg of infliximab was ordered, but administration was delayed because of concerns about insurance reimbursement (because the patient did not have a history of ulcerative colitis). The National Comprehensive Cancer Network guidelines, which showed that tumor necrosis factor alpha–blocking antibodies were indicated for CPI-induced colitis, were presented to the hospital administrator, and infliximab was administered. Within 24 hours, the patient felt remarkably better, and corticosteroids were continued at 120 mg of prednisone by mouth daily. The patient was discharged after 5 days in the hospital, 48 hours after the infliximab administration, without diarrhea. The corticosteroids were tapered over 48 days by 10 mg every 4 days, and a repeat CT scan at week 24 showed a complete response with no evidence of disease, which has been maintained for 2 years.

**CASE 2: MULTIPLE IRAES IN A PATIENT RECEIVING NIVOLUMAB AND IPILIMUMAB**

A 44-year-old woman with a history of stage IV melanoma had liver, lung, and mediastinal disease discovered during a workup for chest pain. Biopsy of a liver lesion showed melanoma that was BRAF wild type and PD-L1 negative. She was treated with nivolumab and ipilimumab combination therapy and received three doses without incident; however, after the second dose, she had a grade 1 elevation of the aspartate aminotransferase (AST) level. A week after the third treatment, she reported that she felt poorly and had a low-grade fever, so she was asked to come to the clinic. Blood tests taken in the clinic showed AST and alanine aminotransferase (ALT) levels greater than 10 times the upper limit of institutional normal, which indicated grade IV toxicity that most likely was an irAE. Blood cultures were negative. The patient was admitted to the observation ward and received 125 mg of intravenous methylprednisolone with intravenous normal saline hydration that evening, and she

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**PRACTICAL APPLICATIONS**

- IrAEs are unique, mechanism-based toxicities of checkpoint inhibition.
- Combination CTLA-4/PD-1 blockade results in a higher rate of irAEs than single agents, and CTLA-4 blockade is associated with more irAEs than PD-1 blockade.
- Virtually all of the symptoms caused by irAEs are reversible with the use of corticosteroids or other immune suppressants.
- Checkpoint inhibitor antibodies increase the risk of a flare of existing autoimmunity.
received an additional dose of methylprednisolone the next morning. The AST and ALT levels were greatly decreased the next morning and the patient felt better, so she was sent home from the observation unit. She was instructed to follow up in clinic every other day for the next week for blood draws to check liver functions, which slowly decreased over the next week. She was placed on 140 mg of prednisone by mouth daily (2 mg/kg), and this dose was tapered down for 2 months. She returned to work as a physical education teacher after 3 weeks of treatment with the corticosteroid taper, and she felt well. She asked to be able to finish the last dose of nivolumab and ipilimumab, but the members of the care team declined. Six weeks after the initiation of corticosteroids, CT scans showed a partial response of all disease. Then, 1 week after the corticosteroids ended, her husband called the care team to report that his wife “just didn’t seem herself,” and he was asked to bring her to clinic. She was seen by a member of the care team, was felt to have a normal mental status examination, and was sent home. Two days later, her husband again called to report that she seemed confused, and he told the care team members that he would bring her back to clinic. At that visit, she was slightly confused, and she seemed to answer questions tangentially. She could not recall her husband’s name, nor the name of the oncologist; however, except for the confusion and mild disorientation, she had a nonfocal neurologic examination. There were no meningeal signs on examination. An urgent MRI of the brain with gadolinium was unrevealing. Thyroid and adrenal function blood tests were normal. She was admitted, and a neurology consult was obtained. A lumbar puncture was performed on the evening of admission, which showed clear fluid, a slightly elevated opening pressure, a mild increase in protein, and 90 white blood cells per cubic millimeter, all atypical in appearance. Cytology was negative, and all infectious and viral titers were negative. She received 250 mg of intravenous methylprednisolone right after the lumbar puncture and then given 125 mg of methylprednisolone twice a day for 2 days. There was gradual improvement in mental status, but the patient remained somewhat disoriented for 72 hours after corticosteroids were started. Prednisone by mouth at 2 mg/kg was started at day 4 after admission; the patient improved and was discharged on day 6 after admission. An oral prednisone taper for 2 months was initiated, and Pneumocystis prophylaxis with oral trimethoprim/sulfamethoxazole was started. Two weeks after discharge, she felt much better and had a normal mental status and neurologic examination in the clinic. She did not recall any details of the recent admission. Two weeks later, her repeat CT scans showed a complete response, and she remains in remission 3 years after the event.

**CASE 3: EXACERBATION OF PRE-EXISTING AUTOIMMUNE DISEASE IN A PATIENT RECEIVING ATEZOLIZUMAB**

A 58-year-old man with a history of scleroderma and stage IV non–small cell lung cancer experienced progression of liver and subcutaneous disease after treatment with frontline chemotherapy, and his tumor biopsy was more than 50% PD-L1 positive by immunohistochemical staining. His scleroderma was manifest by stiffening of, and limitation in, the movement in his hands, thickening and stiffness of the skin of the forearms and lower legs, and mild difficulty swallowing large pieces of solid food, especially meat. His rheumatologist elected to maintain treatment with hydroxychloroquine daily. The patient agreed to be treated with atezolizumab; after three doses, he began to have increased pain in his feet and hands as well as increased stiffness of the hands, and he had difficulty holding a pen as well as insomnia caused by discomfort in his feet. He wished to continue therapy and felt that the subcutaneous lesions were shrinking. At week 12, his CT scans showed a partial response. He continued therapy with an additional four doses of atezolizumab, but he experienced increased fatigue and discomfort in his hands and feet. Corticosteroids were started as 8 mg of methylprednisolone by mouth daily, but he had minimal change in symptoms. He began to have rectal incontinence and some soiling of underwear, which led him to wear a diaper. At week 24, CT scans showed a near complete response of lung cancer, but, at the urging of his oncologist, the patient agreed to stop treatment and increase his immunosuppression therapy. His symptoms began to resolve; at week 36, his scans were stable, but autoimmune symptoms improved (e.g., less fatigue, and he was sleeping better). At week 48, corticosteroid doses had been tapered; he was symptomatically improved and had stable CT scans.

**DISCUSSION**

These three cases illustrate a number of important issues faced by oncology practitioners in the management of irAEs seen with CPI in daily practice.

The first case shows that even the use of high-dose corticosteroids (2 mg/kg) may not induce resolution of symptoms of diarrhea and colitis caused by CPI and that an additional drug, infliximab, should be used for continued grade 3 to 4 diarrhea after a relatively brief trial of corticosteroids. The patient in this case had an initial decrease in diarrhea, which then worsened after 72 hours of corticosteroid therapy and was appropriately treated with a dose of infliximab, the tumor necrosis factor alpha–blocking antibody, at a dosage of 5 mg/kg. Despite resistance by the insurance approvals representative at the outpatient facility, the use of infliximab for CPI-induced colitis refractory to corticosteroids is within National Comprehensive Cancer Network guidelines and is well described in the oncology literature13; when this was pointed out by the oncologist, approval came rapidly. Because infliximab is used acutely for CPI-induced colitis, and may cause resolution of diarrhea and other symptoms of CPI-induced colitis within 24 hours, which is very different from its effects on Crohn disease and ulcerative colitis, in which it is used chronically for months to years and may
induce profound immunosuppression. The high-dose oral corticosteroids should be continued with a slow taper during 45 to 60 days in this case. Newer drugs used to treat colitis, such as vedolizumab, an alpha4-beta7 integrin antibody, have had some success when corticosteroids and infliximab have failed to reverse CPI-induced diarrhea.18 In rare cases, for which resolution of symptoms is slow and multiple immune suppressants have been used without resolution of diarrhea, consideration should be given to placing the patient on total parenteral nutrition, with nothing by mouth, to achieve full bowel rest. In the case presented herein, there was a delay of patient-reported symptoms of diarrhea, which led to dehydration and the need for hospitalization. This experience highlights the importance of good communication between the care team and the patient. At the first hint of diarrhea and cramping pain, the patient should have been seen, symptoms should have been evaluated, and the patient should have been in frequent phone contact with the care team. The close follow-up would have led him to sooner treatment with corticosteroids, which may have been accomplished as an outpatient and would likely have minimized morbidity. In this case, the sigmoidoscopy demonstrated ulceration and erythema, which confirmed the need for re-tapering the steroids and adding infliximab. Findings with endoscopy of the colon range from minimal erythema to profound ulceration, with friability and bleeding of the mucosae. Biopsy often shows cryptitis and diffuse lymphocytic infiltration. Colonoscopy or sigmoidoscopy are generally done, particularly if their results will change the management of the case of colitis.

The second case is illustrative of the complex presentations of multiple irAEs that may occur in patients who receive combination CPI. This case also should indicate to oncology practitioners who use CPI that one must always have a high degree of suspicion that any adverse event may be immune related, even several months after the last dose of drug. With combination therapy, irAEs may appear earlier and last longer, and the likelihood of multiple concurrent and consecutive irAEs is increased compared with CTLA-4 or PD-1/PD-L1 blockade alone.19,20 The prolonged nature of the elevation in AST/ALT can be frustrating for the patient and the care team and may require the use of an additional immunosuppressant, such as mycophenolic acid. Infliximab was not appropriate in this case, because it also can induce hepatotoxicity. The grade 4 elevation in liver function and the prolonged nature of the elevation suggested that additional treatment with a CPI soon after the resolution of the event was not appropriate despite the patient’s request to continue therapy. The refusal of the oncologist and the care team to reinstitute CPI was careful and appropriate. Several weeks after corticosteroids were finished and the patient was back at work, and 2 months after the onset of the episode of grade 4 hepatitis, the subtle mental status changes that occurred should have raised concerns by the care team and led to a more detailed neurologic and cognitive examination. It was only after the patient’s husband insisted on re-evaluation that the care team was able to appreciate the central nervous system changes of encephalitis and institute proper therapy. It was important for the care team to keep an open mind and assemble a proper differential diagnosis to avoid missing a critical irAE, yet rule out other potential causes of the encephalitis that could have been viral, fungal, or even bacterial.

In the third case, the question was whether it was safe to treat a patient with an existing autoimmune disease with CPI. There have been small series and single patient cases published, but no large-scale experience has been described. A recent review of the literature on treatment of 123 patients with existing autoimmune disease who developed cancer with CPI compiled by a group of rheumatologists from a large U.S. cancer center suggested that, although the likelihood of a flare of the underlying disease was 50%, most patients could tolerate single-agent PD-1 blockade, and only 17% of patients had to stop because the exacerbation of symptoms was intolerable.21 A total of 34% of patients had de novo irAEs, mainly colitis and hypophysitis, and no differences were observed in the occurrence of irAEs in those with active or inactive autoimmunity. Corticosteroids were required in 62% of patients, and an additional 16% required increases in, or new, antirheumatologic drugs. Interestingly, the response rate was 50% in those who had an irAE or a flare. Another series included 52 patients with existing autoimmune disease who received anti–PD-1 antibody, with flare of the autoimmune disease in 38% and development of de novo irAEs in 29%.22 Only 12% of patients had to stop CPI therapy. As was seen in the case presented herein, the patient indeed had a flare of scleroderma symptoms and needed additional medicines—including corticosteroids—to manage the effects, yet he continued to receive treatment for 24 weeks until he and his treating physician decided that the effects were intolerable and therapy should stop.

Are there established biomarkers that can be used by practicing oncologists to inform patients about the likelihood of developing irAEs from CPI? The answer is no, because no reliable pretreatment biomarker has accurately predicted the onset of irAEs, and very few studies have explored this issue. One of the few promising approaches is microbiome assessment in patients receiving CPI, because data support the idea that certain anaerobic microbes in the stool are associated with the benefit of CPI with CTLA-4 blockade and PD-1 blockade,23-26 and data also suggest that the type of bacteria within the microbiome may predispose to the development of colitis.27 A number of studies of the serum proteome, peripheral-blood immune cell phenotype, immune cell genome, and epigenome are ongoing to elucidate the mechanisms by which irAEs occur and to predict their onset.

CONCLUSION

The increasing use of checkpoint inhibitory antibodies for cancer will inevitably increase the likelihood that oncology practitioners will have to manage irAEs. Familiarity with the guidelines for irAE management from the European Society
of Medical Oncology\textsuperscript{28} and those soon to be published from ASCO,\textsuperscript{29} as well as good communication between the care team and patients, are crucial elements of the safe management of adverse effects of this class of drug.

References

Tumor-Agnostic Drug Development

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OVERVIEW

Therapies designed to target cancers that harbor specific molecular signatures have reshaped the landscape of oncologic drug development, and advances in next generation sequencing have led to an increase in the identification of these alterations across tumor types. Tumor-agnostic trial designs, such as the “basket trial,” have been developed as an approach to study the efficacy of these treatments and increase patient access, especially for patients whose tumors carry these alterations infrequently. We review key aspects of these genomically enriched trial strategies and their impact on drug development and approval.

The growth in the availability of comprehensive, clinical-grade molecular profiling platforms has led to a rise in the number of predictive biomarkers that have been incorporated into therapeutic paradigms for various cancers. These advances in sequencing have likewise led to an increase in the identification of novel, putative genomic and genetic biomarkers of therapeutic efficacy. Drug development paradigms have had to adapt to a number of challenges in this era, including the decreasing frequencies of these alterations and their identification across multiple tumor histologies. Select clinical trials have thus evolved to incorporate a strong focus on tumor-agnostic drug development, a strategy for enriching for novel targets regardless of tumor site of origin.

Tumor-agnostic patient inclusion on clinical trials is not a novel concept. The classic phase I dose escalation design that attempts to establish a recommended phase II dose is a histology-independent endeavor that only subsequently selects for specific cancers in later-phase testing. The conceptual advance with tumor-agnostic drug development is that trial designs have co-opted this strategy by specifically enrolling molecularly enriched patients to establish efficacy data in phase I expansion cohorts and phase II studies. In general, these studies fulfill the following features that are typical of a “basket trial”: (1) cancers are enriched for one or more molecular alterations, (2) these alterations have a reasonable likelihood of predicting response to a particular therapy based on preclinical functional and/or computational modeling, and (3) these alterations are found across a variety of cancers.

The first generation of basket trials was characterized by the exploration of a validated biomarker in one histology and the exploration of the predictive nature of that biomarker in other cancers. The VE-BASKET trial is an example of such an approach, leveraging the known efficacy of BRAF-directed therapy in BRAFV600E-mutant melanomas. In this phase II, multicenter, international trial, 122 patients with seven different BRAFV600E-mutant nonmelanoma cancers, including gastrointestinal, thoracic, head and neck, thyroid, and hematologic malignancies, were treated with vemurafenib. Noteworthy activity was achieved in non–small cell lung cancer and Erdheim–Chester disease (overall response rates of 43% and 42% respectively), resulting in the U.S. Food and Drug Administration (FDA) granting breakthrough designation for the latter. Moreover, substantial activity was noted in patients with cancers such as pleomorphic xanthoastrocytoma; these patients would otherwise have had no access to targeted therapy in a prospective, histology-specific trial. Other basket trials have since been launched, such as a phase II trial of trastuzumab emtansine for patients with ERBB2-altered cancers. The reported activity of trastuzumab emtansine in ERBB2-mutant lung cancers has since resulted in the inclusion of this drug in the NCCN guidelines for non–small cell lung cancer.

Subsequent trial designs have grown in complexity. Select master protocols, often large, multicenter trials, are composed of several basket cohorts as opposed to investigating a single marker-drug pair. Examples of ongoing trials are the National Cancer Institute MATCH trial, the ASCO TAPUR trial, and the MyPathway trial. The three trials are different in terms of the goals, design, and funding. The NCI sponsored NCI-MATCH trial consists of 25 separate subprotocols, with plans to add more within the coming months, and was designed to evaluate whether patients whose tumors harbor specific gene mutations will benefit from targeted therapies regardless of histology. The trial is...
In many prior clinical trials, context-specific responses to therapy were observed, highlighting that the activity of targeted therapy can be conditioned by the tumor site of origin. Interestingly, two drug development programs have shown that the response to therapy can also largely be histology independent. In a program spanning five different clinical trials, the immune checkpoint inhibitor was found to be active in microsatellite instability (MSI)-high and mismatch-repair deficient (dMMR) tumors across various histologies. These aforementioned trials enrolled a total of 149 patients with either MSI-high or dMMR solid malignancies from 15 different tumor histologies finding an objective response rate of 39.6% (48 partial responses and 11 complete responses) leading to the first FDA approval of a tumor agnostic treatment regimen based off a biomarker. Likewise, the TRK inhibitor, larotrectinib, was evaluated in TRK fusion-positive cancers in a program spanning three different clinical trials including adult, adolescent, and pediatric patients (NCT02122913, NCT02637687, and NCT02576431). An overall response rate of 78% (95% CI, 64%–89%) was observed. This activity was tumor agnostic, age agnostic, and molecularly agnostic (did not differ by upstream fusion partner). The FDA granted breakthrough designation for larotrectinib in TRK fusion-positive cancers in 2017.

The next generation of these trials will must build on the successes of these programs and evolve to address unmet needs. As the multicenter SHIVA trial illustrated, both drug and target must undergo careful vetting prior to initiating a complex trial. The SHIVA trial was a large histologically agnostic trial which screened 716 tumors and identified 293 patients with targetable genetic aberrations involving hormone receptors or the PI3K/AKT/mTOR or RAF/MEK pathways. A total of 195 patients were randomly assigned to treatment (99 to molecularly targeted therapy and 96 onto physician choice therapy). The study was designed with a primary endpoint of progression-free survival (PFS) comparing those on matched targeted therapy and those on physician choice systemic treatment. The study ultimately concluded that there was no benefit in PFS between the experimental group (2.3 months) versus the control arm (2.0 months; HR 0.88, 95% CI, 0.65–1.19, p = .41) finding no benefit to the use of molecularly targeted agents outside of the approved indication. The SHIVA trial has been subject to critique since publication. The trial was lacking in a strong biologic rationale supporting that the genomic biomarker/hormone receptors selected were true actionable drivers that were well matched to potential targeted therapy efficacy. Another noteworthy concern comes from the fact that some of targeted approaches used on protocol were nonselective inhibitors and, as such, call into question the precision of the approach. It also exemplified the importance of utilizing rigorously vetted, and scientifically sound, companion diagnostic tests, to annotate truly actionable findings. The SHIVA study results and design serves as a valuable educational experience for future tumor agnostic trial designs.

Study designs must be flexible and allow a response to data that emerge after trial initiation and, by adopting a

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**PRACTICAL APPLICATIONS**

- In the field of clinical research, the advent of tumor-agnostic trials represents an important step toward discovering biomarkers of response, establishing the effects of context, and elucidating mechanisms of treatment resistance across a variety of cancer types.
- A number of basket trials or master protocols are currently ongoing, including the NCI-MATCH and the ASCO TAPUR trials, in addition to trials sponsored by industry.
- Tumor-agnostic drug development strategies have led and are likely to continue to lead to the integration of genomically informed therapies in the clinic.
“platform trial” strategy, allow marker-drug pairs to exit and be replaced potentially with new drugs or combination therapies.39 For example, the VE-BASKET trial was amended to administer the combination of cetuximab and vemurafenib in BRAFV600E-mutant colorectal cancers after low single-agent vemurafenib activity was observed in these tumors.40 Finally, trials must be willing to adopt a permissive enrollment strategy that allows the careful clinical credentialing of the vast array of genomic alterations identified by comprehensive sequencing, many of which cannot be explored in vitro/in vivo or computationally in a reasonable timeframe.

As we continue to make strides in redefining oncologic diagnoses by incorporating genome-driven information, the importance of new trial designs will continue to grow. Tumor-agnostic drug development programs have taught us that openness to novel strategies may increase our ability to find subpopulations of patients who are likely to benefit from a given therapeutic approach.

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Implementing Precision Medicine Programs and Clinical Trials in the Community-Based Oncology Practice: Barriers and Best Practices

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OVERVIEW

There has been a rapid upick in the pace of oncology precision medicine advancements over the past several decades as a result of increasingly sophisticated technology and the ability to study more patients through innovative trial designs. As more precision oncology approaches are developed, the need for precision medicine trials is increasing in the community setting, where most patients with cancer are treated. However, community-based practices, as well as some academic centers, may face unique barriers to implementing precision medicine programs and trials within their communities. Such challenges include understanding the tissue needs of molecular tests (e.g., tumor, blood), identifying which molecular tests are best used and when tissue should be tested, interpreting the test results and determining actionability, understanding the role of genetic counseling and/or follow-up testing, determining clinical trial eligibility, and assessing patient attitudes and financial concerns. The purpose of this article is to provide guidance to community-based oncology practices currently conducting clinical trials who want to expand their research program to include precision medicine trials. Here, we describe the core components of precision medicine programs and offer best practices for successful implementation of precision medicine trials in community-based practices.

Precision medicine has been discussed for decades, especially in the field of oncology. Precision medicine is an approach to disease prevention and treatment that accounts for variability in the genes, environment, and lifestyle of each person.1 Precision medicine approaches to identifying variability in genetics include the use of multiple testing techniques, including immunohistochemistry, fluorescence in situ hybridization, chromogenic in situ hybridization, flow cytometry, and next-generation sequencing. These techniques are used either in combination or individually to identify molecular abnormalities in a patient’s DNA with the hopes of identifying therapeutic targets.

Historically, patients with cancer have been treated with cytotoxic chemotherapy, which has cured some cancers (e.g., testicular cancer) but also created debates on the overall benefit versus risk. Studies would test single agents, doublets, triplets, and even quadruplets with increasing toxicity and limitations in efficacy. Categorizing patients consisted of organ site of origin and histologic classification. With the increasing development of molecularly targeted therapies, technological advances in genomic testing, and refined techniques for obtaining specimens amenable to genomic testing, precision medicine has become a reality in clinical practice. Molecular assessments now drive therapeutic determinations, which has subsequently decreased the use of chemotherapy and blurred the lines of phenotypic classification (histopathology) with genotypic characterization (genetic testing). For instance, in patients with metastatic, non–small cell lung cancer, approximately 50% of patients’ tumors harbor a molecular abnormality (e.g., EGFR, ALK, ROS1, BRAF, PD-L1) that could be treated with a targeted therapy. For some cancers, it is now expected that the clinical practice of oncology must integrate precision medicine.

Alongside these technology advances, a plethora of trials have been initiated to elucidate molecular pathways that may be involved with cancer development and progression. Examples of precision medicine trials include the BATTLE,2 the National Cancer Institute (NCI) MATCH and M-PACT,3 the ASCO TAPUR4 trials, and several other studies.5 Precision medicine trials invoke new and different challenges in their design and execution, thus requiring new strategies for successful implementation in both the academic and community-based settings.

To have successful precision medicine trials in the community setting, practices first must be committed to developing a multidisciplinary precision medicine program. This article
will focus on enhancing existing research programs in community-based practices to incorporate precision medicine programs and trials. We identify current obstacles to the implementation of programs and trials in community-based oncology practices and suggest best practices for overcoming these barriers.

**BARRIERS TO IMPLEMENTING PRECISION MEDICINE CLINICAL TRIALS**

Barriers to conducting oncology precision medicine clinical trials in the community include the following: molecular testing selection, timing of testing, tissue collection, interpretation of results (actionability), genetic counseling and patient attitudes, clinical trial eligibility, and financial concerns.

**Molecular Test Selection**

Multiple options for molecular testing exist and selecting the appropriate test to use in nonresearch settings is a challenge. It may be difficult for smaller, community-based practices to determine which test is best or to assess test validation. Molecular panel testing in the research setting may be embedded in the study design as an included research cost (e.g., Strata Oncology or the original version of NCI MATCH) or may be ordered before patients are enrolled into a “pragmatic/real-world” clinical trial. When ordered in this setting, the cost of molecular testing falls on the patient or insurer, and study enrollment depends on the molecular inclusion criteria (e.g., ASCO TAPUR and the new version of NCI MATCH). Other research studies may validate the testing centrally (e.g., Novartis Signature with Foundation Medicine).

Research testing with central confirmation may cross-validate testing methodologies. In general, there has been limited testing of molecular panel platforms. Recently, Kim et al found that in 6,897 proficiency testing responses, both laboratory-developed tests and U.S. Food and Drug Administration–approved companion diagnostics exceeded 97% accuracy combined across all comparable molecular oncology proficiency testing samples. However, there may be greater discordance with liquid biopsy testing. Clinical trials that directly assess solid versus liquid biopsies and utility for treatment decision-making and monitoring are needed.

**Timing of Molecular Testing**

For nonresearch molecular panel testing or real-world testing, many patients have historically had to wait 14 days after the biopsy according to the “14-day rule” (i.e., the laboratory date of service for clinical laboratory and pathology specimens, as outlined in the Code of Federal Regulations). This federal regulation does not require physicians to wait 14 days to send out a specimen for molecular panel testing, but if the test was ordered within 14 days, the molecular panel testing company could not directly bill Medicare and had to bill the location where the biopsy procedure occurred (e.g., clinic, hospital). The hospital or clinic could then bill Medicare to obtain reimbursement. This complicated payment process resulted in unnecessary delays in care or avoidance of test ordering. Concern regarding this antiquated rule prompted the Centers for Medicare & Medicaid Services to review the policy and ultimately change it. As of January 2018, the 14-day rule no longer applies to DNA-only tests (e.g., Foundation Medicine), but it still holds true for tests that include immunohistochemistry assessment (e.g., Caris Life Sciences). The 14-day rule also still applies to patients who are hospitalized during the time of the sample acquisition (although this policy may be changing). Updated guidelines on molecular testing for patients with lung cancer specify a 10-day window from sample receipt to test result as an acceptable turnaround time for molecular testing for targeted tyrosine kinase inhibitors; however, considering the time it takes to schedule and obtain tissue, the time to obtaining molecular test results can often be much longer.

**Tissue Collection**

The quantity and quality of tumor specimens are not always optimal. The quantity of tissue recommended for molecular testing ranges by test methods. For example, next-generation sequencing of DNA requires a formalin-fixed paraffin-embedded block (5 x 5 mm) or 10 to 15 unstained slides with a minimum of 20% malignant origin or four to six cores from a needle biopsy (using an 18-gauge needle). Additional tumor tissue is recommended for RNA next-generation sequencing or other tests (e.g., immunohistochemistry, chromosome in situ hybridization). For some tests (e.g., MI Profile; Caris Life Sciences, Phoenix, AZ), 40 or more slides may be requested. A formalin-fixed paraffin-embedded block is preferred for most tests. This amount is not always possible to obtain because of the size or position of the tumor.
In addition to the quantity of tumor needed, quality also matters. In samples obtained from bone, common decalcification procedures may seriously affect DNA/RNA-based testing, whereas ethylenediaminetetraacetic acid–based decalcification may be preferred for nucleic acid extraction.\(^\text{18,19}\)

In addition, processing of tissue specimens may be suboptimal. For example, for patients undergoing a colonoscopy, the specimen could not be used for Foundation Medicine testing if the biopsied tissue were processed with zinc formalin. Information from Caris Life Sciences suggests that this results from divalent cations inhibiting the polymerase chain reactions necessary for molecular diagnostics.\(^\text{20}\)

Tumor tissue for molecular testing remains the gold standard for obtaining genomic information; however, obtaining new tumor tissue is not always feasible. Use of archived tissue may be possible in cases in which obtaining new tumor tissue is not feasible, but providers must consider that the archived tissue may be from years prior and/or obtained prior to the patient receiving multiple lines of therapy. Specimen age and fixation methods are important and can impede testing. As a general suggestion, specimens older than 10 years may suffer from degradation. Liquid biopsy testing for ctDNA or cell-free DNA has great potential for use when tumor tissue is not available but currently lacks validation in broader settings.

**Interpretation of Actionability**

A molecular alteration that is “actionable” is often defined differently in the clinical setting as opposed to the research setting. Various evidence scoring categories have been proposed, including those from Beltran et al\(^\text{21}\) (categories 1–3, in which category 1 is abnormality with a targeted therapy available) and the 2017 Joint Consensus Recommendation of the Association for Molecular Pathology, ASCO, and College of American Pathologists\(^\text{22}\) (levels A–D, in which A indicates the biomarker can predict response/resistance or is included in professional guidelines as therapeutic, diagnostic, or prognostic for specific tumor types). Beltran et al\(^\text{21}\) noted 16 somatic alterations per patient in whole-exome sequencing. In their analysis, more than 90% of patients had clinically or biologically pertinent results with recommendations from an MTB, but only 5% of patients received precision medicine–guided treatment.

In the context of a clinical trial, targetable molecular alterations are generally well defined. One such example is NCI MATCH arms A (EGFR mutation; drug: afatinib), C1 (MET amplification; drug: crizotinib), and C2 (MET exon 14 splicing alteration; drug: crizotinib).\(^\text{21}\) If a patient is enrolled in a research study, then the molecular testing is reviewed per the study parameters. In both the NCI MATCH and ASCO TAPUR trials, higher rates of patient matching to targeted therapies have been reported (18% and 66%, respectively)\(^\text{24,25}\) compared with the study by Beltran et al that reported a lower rate of patients matched to precision medicine treatments.\(^\text{21}\)

If molecular testing is done prior to treatment selection or clinical trial evaluation, then MTBs, computer flags for potential trials, and clinical decision support tools are emerging mechanisms to help facilitate accrual.\(^\text{26}\) At Levine Cancer Institute, a variety of tools are used to facilitate action on targetable alterations. In addition to a consultative MTB, Levine Cancer Institute has developed the LCI Integrated Knowledge database, which provides an automated synopsis of molecular alterations and potential clinical trial matches for each patient with genomic test results. In addition, providers are notified by email that a report has been returned and the email provides links that allow the provider can view the report and schedule a consultative MTB review. Providers can use the study summary pages embedded in the EAPathways electronic accessible clinical pathways tool to gain quick knowledge about the study rationale, objectives, and eligibility criteria.\(^\text{27}\)

**Clinical Trial Eligibility**

Investigators initiating precision medicine trials should carefully consider molecular testing needs when designing studies.\(^\text{28-30}\)

For many trials, tumor tissue for molecular testing is required. This requirement can limit enrollment in trials, especially in community-based settings where patients may not wish to travel to another facility for a biopsy or in certain tumor types where obtaining quality tissue is a challenge. Precision medicine trial investigators should consider relaxing tissue requirements by making fresh tumor biopsies optional or requiring only archival tissue when feasible and when the study design permits. Precision medicine trial investigators may also consider including liquid biopsies in addition to a tumor biopsy or when tumor tissue is not available. These approaches would increase patient eligibility for precision medicine trials, a strategic goal of ASCO, and help grow these programs, thus increasing patient access to precision medicine trials.

**Genetic Counseling and Patient Attitudes**

Molecular panel testing can generate somatic information that is potentially targetable, as well as germline information that can have implications for both the patient and his or her relatives. BRCA1/2 alterations are examples of both. Working with genetic counseling services (e.g., as a local site service, via telemedicine, or as part of a clinical trial support network) is becoming increasingly important. Tumor variants of unknown importance versus germline classification may be imputed by allele frequency (queryable from some companies) or via comparison testing of normal, noncancer material from the patient. As some diseases are found to be increasingly associated with germline alterations (e.g., prostate and breast cancers) and new associations are elucidated, combining testing with genetic counseling is a critical element of PM treatment. An ancillary study to NCI MATCH called COMET (Communication and
Education in Tumor Profiling) is examining the effects of providing genetic testing education to patients with cancer and assessing how this affects their knowledge and stress levels.31

**Financial Concerns**

Patient financial constraints also present challenges to the community-based precision medicine program. Some practices may conduct precision medicine under the auspices of umbrella research protocols. These protocols allow for data sharing in return for reduced testing costs, but they often require partnerships with the genomic testing company that smaller, community-based practices may not have. Large panel genomic testing may come with high out-of-pocket costs for patients, although prices are decreasing. Recent national Medicare coverage announcements and the U.S. Food and Drug Administration’s approval of the FoundationOne F1CDx next-generation sequencing–based in vitro diagnostic test (Foundation Medicine, Cambridge, MA) allow this test to be administered to Medicare beneficiaries with recurrent, metastatic, or advanced stage IV non–small cell lung cancer, melanoma, breast cancer, colorectal cancer, or ovarian cancer.32 Additionally, patient assistance programs are available to support the use of these tests; however, even with these programs, the cost of large panel molecular tests may place them out of reach for some patients.

Practices also have financial concerns. Creating a business plan, selling the plan to other practice partners, and setting up the networks and infrastructure to support precision medicine therapy and trials is challenging. Precision medicine programs involve significant time and resources for successful implementation. It is important to have buy-in from practice partners and create value for patients; otherwise providers and patients will not be engaged.

There are conflicting opinions with regard to the value of precision medicine,33,34 and practices should consider not just the monetary cost involved with developing these programs and conducting trials. There are also indirect benefits, such as the ability to deliver cutting edge therapies and higher quality care to patients.

**STRATEGIES FOR IMPLEMENTING SUCCESSFUL PRECISION MEDICINE PROGRAMS AND CLINICAL TRIALS**

Implementing successful precision medicine trials is dependent on a successful precision medicine program. These programs require a multidisciplinary commitment to assembling a unique foundation for conducting and evaluating genomic testing (Fig. 1). As precision medicine programs require direction and resources from many stakeholders, it is imperative that all parties are committed to the program’s success.

A fundamental element of a successful program is the collaborative relationship between the clinical and research departments in the organization. Given the multifaceted, complex, and quickly changing landscape in precision medicine, it is imperative to establish early and frequent communication amongst all stakeholders, but especially between the program leadership team, director, and clinical trial leadership. Without the dedication of shared resources, the program is likely to remain in a silo with implementation of precision medicine trials, the driver of precision medicine, at a disadvantage.

In addition to the collaborative relationships between the clinical and research teams, successful precision medicine programs are composed of dedicated personnel, access to facilities and providers practicing across multiple disciplines, advanced technology tools, and partnerships between the clinical operations team, research team, and genomic profiling companies. Community-based practices may find it more challenging to create a precision medicine program compared with traditional academic institutions with extensive resources, but with proper planning and collaborative work it is feasible. Most patients with cancer (85%) are treated in the community setting, providing ample opportunity to impact precision medicine trial accrual through successful operationalization of a community-based precision medicine program.35 Strategies utilized by institutions with successful precision medicine programs and trials are described in this section and can be applied at community-based practices.32,36

**Personnel**

Identifying the stakeholders and personnel is a key strategy for implementing a successful precision medicine program. Some practices may find it useful to initiate the program under the auspices of an umbrella research protocol, which provides for feasibility testing of operational workflows, collection of data for early internal analysis regarding utility, and development of a precision medicine trial portfolio. When this is the approach, coordination of protocol development and implementation, tissue acquisition, sample shipping, molecular testing result return, and review of molecular testing results in a molecular tumor board is critical to timely patient care and enrollment in precision medicine trials. As such, managing the complexities of a precision medicine program is best served by a multidisciplinary team that includes dedicated leadership.

**Leadership team.** A precision medicine program leadership team should be identified to define the overall direction for the program based on current state-of-the-science and treatment developments. The leadership team should consist of physicians experienced in conducting precision medicine trials and other experts, such as molecular biologists, computational biologists, and geneticists. Lead physicians advocate for precision medicine clinical trial options with collaborative partners, ultimately enhancing the adoption of testing and targeted treatment within the program. Internally, the lead physicians are positioned to support the request for additional resources and foster the engagement from that clinical administration that is needed for long-term integration of precision medicine trials into clinical care in the community setting. It is the role of the leadership team to recruit and engage all the relevant practice stakeholders. Physicians and other experts on the precision medicine program leadership team should provide continual education and support, to providers practicing precision medicine and other program members, because the field changes rapidly.
**Director.** To augment the leadership of the team, practices may consider hiring a director to guide day-to-day activities early in the development of the precision medicine program. A director with clinical, research, and business experience expedites processes, ensures that the program’s depth and breadth is maximized, and engages with vendors. The director interacts with clinical research coordinators, clinic nurses, preauthorization specialists, schedulers, billing specialists, biospecimen repository technicians, and pathologists, along with vendors, and can bridge the research and clinical continuum required to successfully conduct a precision medicine trial. Routine meetings with key stakeholders, led by the director and documented, are key in the timely identification and mitigation of issues, provide reference material for troubleshooting as precision medicine trials are adopted on a wider scale, and support oncologists’ decisions for off-label drug use.

**Biospecimen repository and pathology team.** If resources for establishing a biospecimen repository and hiring associated staff are available, this should be pursued, as having a dedicated biospecimen repository and team is an efficient approach to coordinating specimen retrieval, processing, and shipping, greatly reduces the workload of the study coordinators, and standardizes process across multiple practices. The biospecimen repository team can serve as an additional resource for treating physicians and investigators on many issues such as education, test ordering, and billing and reimbursement. Pathologists are an integral part of the precision medicine program, providing genomic testing outside of commercial vendors. Pathology assistants trained in specimen preparation are also encouraged.

**Molecular Tumor Boards**
Molecular testing reports are unique to the vendor and can be ambiguous for first-time users or providers with limited experience. Much like the multidisciplinary approach to obtaining the tissue, the results are best analyzed in a multidisciplinary setting. If resources are available at community-based practices, establishment of a local MTB allows precision medicine program personnel from various areas, along with providers who may be utilizing precision medicine approaches in the clinic, to come together. If establishing a local MTB is not feasible, community-based practices can participate in virtual MTBs such as those offered as part of research studies (e.g., ASCO TAPUR). If local or study-specific MTBs are not available, websites like Heailio’s Learn Genomics37 or the ASCO University Molecular Tumor Board38 can provide static MTB cases for providers to review. MTB cases currently residing on the Learn...
Genomics website include cases focused on gastric and lung adenocarcinoma. In addition to real-life precision medicine examples, the Learn Genomics website also serves as a genomics educational resource for providers and patients.

A local MTB is most successful when it is composed of personnel described previously and other physicians representing medical oncology, radiation oncology, radiology, and pathology, genetic counselors, clinical research coordinators, and nurse navigators. The MTB provides support for developing and initiating a timely treatment plan for precision medicine trials and offering precision medicine options to patients not seeking clinical trials. When reviewing MTB cases, compliance with Healthcare Insurance Portability and Accountability Act (HIPAA) requirements should be ensured. Weekly MTB meetings may be sufficient for a small precision medicine program, with the option of moving to twice a week as volume increases. The frequency of the MTB, if used prospectively, must be assessed periodically to ensure that results and discussion of the case are not being delayed unnecessarily, which creates a setback in delivering timely patient care. The frequency of MTB meetings should depend on the number of cases to review. In our experience, one hour typically consists of up to three detailed, physician-led patient cases and 15 brief, director-led overviews. The precision medicine director must commit considerable time and effort up front to review the results of genomic testing panels, prior treatment history, and potential matched clinical trials. MTBs also serve as a venue for educating providers about mechanisms for obtaining molecular testing (e.g., research options or low-cost programs), which can help reduce disparities in access to testing.

Biospecimen Acquisition and Genomic Results Workflows

Processes regarding biospecimen acquisition and reporting of genomic results are important to successful programs. Precision medicine trials require molecular testing of tumor and other specimens (e.g., blood) to identify genomic alterations of interest for study eligibility, making access to quality specimens paramount. The requirement for a new biopsy to obtain tissue is often dependent on the study design. Alternatively, archival tissue may be acceptable for molecular testing in other studies. When existing tissue may be used, the study team should verify the type and quantity of tissue needed per protocol and communicate with the pathology department to ensure that adequate tissue exists and can be released per institutional guidelines. In any case (new biopsy or archival specimen), the study team must develop a process to notify the pathology department of the testing request, facilitate the shipment of tissue to the testing vendor, and receive results for physician review.

Practices may wish to consider having the interventional radiology team perform a preliminary review of the lesions prior to scheduling the biopsy in order to allow them to triage which cases may be appropriate for a new biopsy. For cases that are not suitable, archived tissue or a liquid biopsy may be feasible. For cases that require a new biopsy for study or standard-of-care treatment purposes, the workflows developed by the precision medicine director and study team contribute to the successful acquisition of tissue. Access to the interventional or operative suite and associated provider, either by the study coordinator or biospecimen repository team, further drives the feasibility of obtaining enough high-quality tissue in an acceptable timeframe. Ensuring that the study team has the appropriate contacts in the scheduling, billing, and preauthorization office dramatically reduces the time from biopsy order to completion. Educating the ancillary teams and collaborating on creating workflows should be a primary task of the precision medicine director and study team at the outset of the project.

Technology

Data collection and informatics. Precision medicine trials, much like other clinical trials, are data driven. However, the amount of data and the coordination of review and storage of data are much more complex, in part because of the volume generated with molecular testing. Practices embarking on the inclusion of precision medicine trials in the community setting should evaluate current and future data-handling procedures, especially in terms of storing results in the electronic medical record. Because of the complexity of molecular data, bioinformaticians are an important component to precision medicine trials.

To reduce data entry error and the amount of time and effort that study coordinators need for data abstraction, community-based practices that wish to develop precision medicine programs and conduct trials may consider investing resources in the development of automated data transfer processes for molecular data. If automated molecular data transfer solutions are not possible, then manual abstraction can be used. However, because of the detailed nature of this type of data abstraction, an outlined, multiple-check quality assurance approach is suggested.

The precision medicine clinical trial menu may include investigator-initiated trials, which present unique operational considerations. A key issue for investigator-initiated precision medicine trials, beyond data handling of molecular testing results, is the collection, maintenance, and storage of clinical and outcomes data. As the program expands, interest surrounding the mutations identified across the patient population will likely arise (from both the research and the clinical arms of the organization), especially when new mutations are identified that become targetable. Collecting data in an electronic data capture tool with discrete fields allows for future data queries of molecular results and allows for data quality checks.

A multistakeholder report recently published by Conley et al outlines core clinical data elements that investigators conducting precision medicine studies should consider. Table 1 describes both the core clinical data elements described by Conley et al as well as additional data elements investigators may wish to include. For example, some investigators may wish to include data on adverse events or patient-reported outcomes data to elucidate the relationships between targeted therapies and these events.
**TABLE 1. Data Elements to Consider for Inclusion in Precision Medicine Trials**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Data Element</th>
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<tbody>
<tr>
<td>Demographics</td>
<td>Sex*</td>
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<tr>
<td></td>
<td>Ethnicity*</td>
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<td></td>
<td>Race*</td>
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<td></td>
<td>Date of birth*</td>
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<tr>
<td>Medical history</td>
<td>Prior malignancies*</td>
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<tr>
<td></td>
<td>Date of diagnosis of prior malignancies*</td>
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<tr>
<td>Treatment history (if not first)</td>
<td>Treatments administered</td>
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<tr>
<td></td>
<td>Start and stop dates of treatments administered</td>
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<tr>
<td>Physical examination at diagnosis</td>
<td>Height and weight*</td>
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<tr>
<td></td>
<td>Performance status*</td>
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<td></td>
<td>Date of physical examination</td>
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<tr>
<td>First diagnosis of interest</td>
<td>Basis of diagnosis*</td>
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<td></td>
<td>Cancer site and histology*</td>
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<td></td>
<td>Stage and grade*</td>
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<td></td>
<td>Date of diagnosis*</td>
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<td></td>
<td>Site and type of tissue sampling*</td>
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<td></td>
<td>Prognostic biomarkers*</td>
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<td>Molecular diagnostics</td>
<td>Tumor vs. blood biopsy</td>
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<td></td>
<td>Specimen collected (if tumor)</td>
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<td></td>
<td>Test method</td>
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<td></td>
<td>Date of specimen collected</td>
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<td>Date of test result</td>
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<td></td>
<td>Genomic alteration(s), including variants of unknown importance</td>
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<td></td>
<td>MAF or amplification present</td>
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<td>MTB assessment</td>
<td>Date case is reviewed by MTB</td>
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<td></td>
<td>MTB determination of “actionable alterations”</td>
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<td></td>
<td>MTB recommended therapy</td>
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<td></td>
<td>MTB recommendation for follow-up genetic counseling</td>
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<tr>
<td>Treatment episode</td>
<td>Therapeutic agent and/or modality*</td>
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<td></td>
<td>Intent of treatment*</td>
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<td></td>
<td>Treatment start and stop dates</td>
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<td></td>
<td>Reason for treatment discontinuation*</td>
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<tr>
<td>Outcomes</td>
<td>Disease response*</td>
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<td></td>
<td>Method of response evaluation*</td>
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<tr>
<td></td>
<td>Sites of progression/recurrence*</td>
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<tr>
<td></td>
<td>Date of response evaluation</td>
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<tr>
<td>Adverse events</td>
<td>CTCAE event</td>
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<tr>
<td></td>
<td>Event grade</td>
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<td></td>
<td>Date of CTCAE event</td>
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<tr>
<td></td>
<td>Outcome and treatment in response to CTCAE event</td>
</tr>
<tr>
<td>Patient-reported outcomes</td>
<td>PRO-CTCAE event</td>
</tr>
<tr>
<td></td>
<td>PRO-CTCAE frequency, severity, interference</td>
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<tr>
<td></td>
<td>Date of PRO-CTCAE event</td>
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</table>
Virtual molecular tumor boards. Although housing large data sets may be a challenge, perhaps the most important hurdle in operationalizing precision medicine trials is the appropriate review of molecular testing results. In some community practices, the providers and staff included on the MTB are located in separate facilities. For those precision medicine providers, a virtual MTB should be used to foster collaborative, real-time dialogue between providers in different geographic locations. Ideally, a videoconference with presentation capabilities can be used at each participating practice. Projecting molecular testing reports, as well as reviewing radiologic and/or pathologic images, aids in facilitating the discussion. An interactive MTB also provides a portal for continued education of providers as testing capabilities change and information regarding novel pathways or treatments becomes available. Furthermore, discussions around general operations and challenges of the precision medicine program, as well as needs for successful precision medicine trial enrollment and/or portfolio expansion, are best suited for the MTB in which key stakeholders are all present at the same time.

CONCLUSION

Establishing a high-quality precision medicine program that includes precision medicine clinical trials at community-based practices that are already conducting clinical research is feasible with planning and resources. Practices may consider introducing a precision medicine program and corresponding clinical trial menu that is narrow in scope and then expand the program. As large genetic panel testing increases and the need for counseling moves from highly resourced large academic centers to community-based practices, where 85% of patients with cancer are treated, we must continually assess how precision medicine is implemented, both in clinical trials and off study, and share best practices.

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ERSEK ET AL


Combination Immunotherapy Development in Melanoma

Alexander M. M. Eggermont, MD, PhD, Marka Crittenden, MD, PhD, and Jennifer Wargo, MD, PhD

OVERVIEW

Melanoma has been the most important cancer to drive immunotherapy development of solid tumors. Since 2010, immunotherapy has been revolutionized by the concept of breaking tolerance. It represents a major paradigm shift and marks the beginning of a new era. The impact of the first immune checkpoint inhibitors, anti–CTLA-4 and anti–PD-1/anti–PD-L1, is unprecedented. In 7 years, it transformed advanced-stage melanoma into a curable disease in over 50% of patients. Another major step has been the development of the combination of BRAF inhibitors plus MEK inhibitors in the treatment of BRAF-mutant melanomas. For the treatment of advanced disease, approvals were obtained for the immune checkpoint inhibitors ipilimumab (2011), nivolumab (2014), pembrolizumab (2014), the combination ipilimumab plus nivolumab (2015), and the oncolytic virus vaccine laherparepvec (2015). The combination dabrafenib plus trametinib for BRAF-mutant melanoma was approved in 2014, with similar success for other BRAF plus MEK inhibitor combinations. Because of its unique therapeutic index (high efficacy and low toxicity) anti–PD-1 agents (nivolumab and pembrolizumab) have now been placed at the center of practically all combination therapy development strategies in melanoma. Anti–PD-1 agents are the central molecule for combinations with a great variety of other immunotherapeutics such as immune checkpoint inhibitors, agonists, IDO inhibitors, macrophage polarizing agents, monoclonal antibodies, vaccines, targeted agents, chemotherapeutics, radiation therapy, and even microbiome modulators.

IMMUNE CHECKPOINT INHIBITORS

Anti–CTLA-4

Monoclonal antibody blocking of CTLA-4 leads to breaking immune tolerance and can induce tumor regression. The anti–CTLA-4 antibody ipilimumab (3 mg/kg) was approved in 2011 for advanced-stage melanoma based on randomized controlled trial (RCT) results showing that ipilimumab alone or combined with peptide vaccination increased survival by 33% compared with vaccination alone.1 Ipilimumab at 10 mg/kg combined with dacarbazine did not further increase the long-term overall survival (OS) of 20% compared with ipilimumab alone2-4 or with tremelimumab alone.5 The efficacy in patients with brain metastases was reported as well.6 Since responses can occur after initial tumor progression or appearance of new lesions, immune-related response criteria were developed.7,8 In 2016, RCT results demonstrated that the 10 mg/kg dose increased OS compared with the 3 mg/kg dose (31% vs. 23% at 3 years), at the cost of twice the grade 3 to 4 toxicity rate (34% vs. 19%) and drug-related death rate (1.2% vs. 0.6%).9 The immune-related adverse event (AE) profile of ipilimumab at 3 mg/kg is already complex with colitis, hepatitis, hypophysitis, and rare cases of myocarditis and neutritis syndromes, indicating that combinations with ipilimumab at 3 mg are not simple to develop. No robust baseline predictive biomarkers have been established for clinical decision-making, although the combination of high levels of lactate dehydrogenase, C-reactive protein, myeloid-derived suppressor cells, and regulatory T cells, and low counts of lymphocyte and eosinophile are indicators of poor outcome.10

Combination Therapies With Ipilimumab

Various combinations of ipilimumab with other immune-modulating, antiangiogenic, chemotherapeutic, or targeted agents have been investigated or are under evaluation, but nivolumab and pembrolizumab have taken center stage in development of combination therapies. Guiding principles for combination treatment designs could be to use drugs or radiotherapy that lead to immunogenic cell death.11,12

Chemotherapy

Dacarbazine. An RCT comparing dacarbazine compared with dacarbazine plus ipilimumab at 10 mg/kg in first-line advanced-stage melanoma showed a survival benefit for the combination.2 Long-term survival in the combination arm was 20%, indicating that the combination is not better than ipilimumab alone.3,4

Fotemustine. In a phase II trial, 86 patients with advanced-stage melanoma, of whom 20 had asymptomatic brain
metastases, received ipilimumab induction treatment at 10 mg/kg and 100 mg/m² fotemustine weekly for 3 weeks and then maintenance treatment every 3 weeks.\textsuperscript{13,14} Forty patients (46.5\%) achieved disease control, as did 10 patients with brain metastases (50\%), with grade 3 or higher AEs in 55\%. Carboplatin/taxol. Thirty patients with advanced-stage melanoma received ipilimumab and carboplatin/taxol. Best overall response and disease control rates were 27\% and 57\%, with 13\% grade or higher 3 AEs. Median OS was 16.2 months.\textsuperscript{15}

\begin{itemize}
  \item \textbf{Antiangiogenic Agents}
  \begin{itemize}
    \item \textbf{Bevacizumab.} In a phase II study, 46 patients with metastatic melanoma were treated in four dosing cohorts of ipilimumab (3 or 10 mg/kg) with four doses at 3-week intervals and then every 12 weeks, and bevacizumab (7.5 or 15 mg/kg) every 3 weeks.\textsuperscript{16} Best overall response: eight partial responses and 22 cases of stable disease, with a disease-control rate of 67.4\%. Median survival was 25.1 months. These results merit further exploration.
  \end{itemize}

\begin{itemize}
  \item \textbf{Cytokines}
  \begin{itemize}
    \item \textbf{Interleukin-2.} The most mature data on this combination were shown among a 36-patient cohort treated at the National Cancer Institute Surgery Branch.\textsuperscript{17} There were six complete responses (17\%), which was higher than the 6\% to 7\% complete response rate in 141 patients treated with ipilimumab alone or in combination with gp100 vaccination
    \begin{itemize}
      \item \textbf{Interferon-alpha.} A phase II trial in 35 patients evaluated the combination of high-dose interferon with tremelimumab.\textsuperscript{18} The overall response rate was 24\% (four complete responses and five partial responses) and 38\% with stable disease, with a median progression-free response of 6.4 months and a median OS of 21 months, suggesting additive antitumor activity. The combination of pegylated interferon and ipilimumab in 27 evaluable patients yielded four complete responses, eight partial responses, four cases of stable disease, and 13 PDs for a response rate of 40\% with grade 3 to 4 toxicities in 45\%.\textsuperscript{19}
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Granulocyte-macrophage colony-stimulating factor.} A randomized phase II trial in 245 patients with advanced-stage melanoma, compared ipilimumab plus granulocyte-macrophage colony-stimulating factor (GM-CSF; sargramostim) with ipilimumab alone.\textsuperscript{20} Patients received ipilimumab at 10 mg/kg, on day 1 plus sargramostim, 250 μg, on days 1 to 14 of a 21-day cycle or ipilimumab alone. Ipilimumab treatment included induction for four cycles followed by maintenance every fourth cycle. At a median follow-up of 13.3 months, OS was superior for combination treatment (17.5 months versus 12.7 months) and the 1-year survival rates were 68.9\% versus 52.9\%, without differences in progression-free survival (3.1 months for both arms).
  \end{itemize}

\begin{itemize}
  \item \textbf{Vaccines}
  \begin{itemize}
    \item \textbf{Talimogene laherparepvec.} Talimogene laherparepvec (T-VEC) is a herpes simplex virus type 1-derived oncolytic immuno-therapy designed to selectively replicate within tumors and produce GM-CSF. Intratumoral administration of T-VEC was compared with subcutaneous administration of GM-CSF in patients with stage IIIB to IV melanoma in a RCT.\textsuperscript{21} With grade 3 to 4 events in less than 2\% of the 436 patients, the durable response rate (> 6 months) was higher with T-VEC (16.3\%) than GM-CSF (2.1\%). Overall response rates were 26.4\% compared with 5.7\%, and median OS was 23.3 months versus 18.9 months (hazard ratio 0.79; p = .051) for T-VEC and GM-CSF, respectively. T-VEC was approved by the U.S. Food and Drug Administration in 2015.
    \begin{itemize}
      \item \textbf{T-VEC with ipilimumab.} A randomized phase II trial comparing ipilimumab plus T-VEC with ipilimumab alone demonstrated that the overall response rate in the combination arm was significantly higher than in the ipilimumab-alone arm (39\% vs. 18\%; p < .002), with grade 3 or higher AEs in 45\% vs. 35\%.\textsuperscript{22}
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{BRAF and MEK Inhibitors}
  \begin{itemize}
    \item Combinations of BRAF inhibitors and MEK inhibitors with immune checkpoint inhibitors such as anti-CTLA are theoretically attractive, but have in practice proven to be not so simple to develop. A phase I trial combining vemurafenib and ipilimumab was stopped early because of several cases of grade 3 to 4 hepatitis.\textsuperscript{23} A phase I trial with dabrafenib and ipilimumab did not reveal a high rate of severe hepatitis. However, the combination of dabrafenib plus trametinib with ipilimumab was stopped after seven patients because of severe colitis in three patients; no extension cohort was planned.\textsuperscript{24}
    \begin{itemize}
      \item \textbf{Anti–PD-1 and Anti–PD-L1}
      \begin{itemize}
        \item The immune checkpoint PD-1 is expressed on many tumor-infiltrating lymphocytes in response to inflammation. The engagement of PD-1 on the lymphocyte by PD-L1 on melanoma cells and PD-L1-expressing components of the tumor infiltrate downregulates T-cell function.\textsuperscript{25} Avoiding this by the use of anti–PD-1 and anti–PD-L1 antibodies has been remarkably successful, both in terms of response rates (30\%–45\%) and durability (2–3 years) in melanoma,\textsuperscript{26,27} even after discontinuation,\textsuperscript{28} and in terms of a very favorable toxicity profile in comparison with anti–CTLA-4 antibodies.\textsuperscript{29}
      \end{itemize}
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Remarkable success:}
  \begin{itemize}
    \item \textbf{Interleukin-2.} The most mature data on this combination were shown among a 36-patient cohort treated at the National Cancer Institute Surgery Branch.\textsuperscript{17} There were six complete responses (17\%), which was higher than the 6\% to 7\% complete response rate in 141 patients treated with ipilimumab alone or in combination with gp100 vaccination
    \begin{itemize}
      \item \textbf{Interferon-alpha.} A phase II trial in 35 patients evaluated the combination of high-dose interferon with tremelimumab.\textsuperscript{18} The overall response rate was 24\% (four complete responses and five partial responses) and 38\% with stable disease, with a median progression-free response of 6.4 months and a median OS of 21 months, suggesting additive antitumor activity. The combination of pegylated interferon and ipilimumab in 27 evaluable patients yielded four complete responses, eight partial responses, four cases of stable disease, and 13 PDs for a response rate of 40\% with grade 3 to 4 toxicities in 45\%.\textsuperscript{19}
    \end{itemize}
  \end{itemize}

\begin{itemize}
  \item \textbf{Clinical Applications}
  \begin{itemize}
    \item \textbf{Melanoma has been the most important cancer to drive immunotherapy development of solid tumors.}
    \item The first immune checkpoint inhibitors advanced melanoma into a curable disease in over 50\% of patients.
    \item The immune checkpoint inhibitors ipilimumab, nivolumab, pembrolizumab, ipilimumab with nivolumab, and the oncolytic virus vaccine laherparepvec have been approved to treat advanced melanoma.
    \item Anti–PD-1 agents nivolumab and pembrolizumab have now been placed at the center of combination therapy development strategies in melanoma due to their high efficacy and low toxicity.
  \end{itemize}

\end{itemize}
In only a few years, phase I to III trials resulted in rapid approval of nivolumab and pembrolizumab for advanced melanoma in 2014 and in many other tumor types in the years thereafter. PD-L1 expression in the tumor is a good biomarker for response for monotherapy with either agent, but even in patients who are PD-L1 negative, it is more effective than chemotherapy or ipilimumab. It is the first-line drug of choice for all patients with metastatic melanoma, with the exception of those with bulky, rapidly progressive BRAF-mutant melanoma. Yet, a wide variety of immune-related AEs can be seen at low frequencies. Excellent overview articles discuss the diagnosis and treatment of these toxicities. Indicators at baseline for good outcome with anti–PD-1 treatment are low M-category, low lactate dehydrogenase, high lymphocyte and eosinophil counts, and high PD-L1 expression. Overall anti–PD-1 and anti–PD-L1 antibodies, because of their ideal therapeutic index, have taken central stage in combination development strategies that we will summarize below. Immuno-oncology therapies that failed as monotherapeutic approaches, such as cytokines, vaccines, and IDO inhibitors to mention a few, now are developed in combination with anti–PD-1 or anti–PD-L1 agents with remarkable promise!

**Anti–PD-1 Plus Anti–CTLA-4 Combination Therapy**
The rationale to combine these two checkpoint inhibitors is that they have different mechanisms of action, with anti–CTLA-4 mainly acting in the lymph node compartment at restoring the induction and proliferation of activated T cells, and with anti–PD-1 mainly acting at the periphery at the tumor site, preventing the neutralization of cytotoxic T cells by PD-L1 expressing tumor and plasmoid dendritic cells in the tumor infiltrate. The first report in 2013 already indicated that the combination is associated with clearly increased response rates up to 50% to 60%, with an increased complete response rate of around 20% and an increase in near-complete responses. A randomized phase II trial of nivolumab plus ipilimumab compared with ipilimumab (2:1) demonstrated, at a median follow-up of 24.5 months, a 2-year OS of 63.8% for the combination compared with 53.6% for ipilimumab alone. Combination therapy was associated with grade 3 or higher AEs in 54% of patients versus 20% of patients for ipilimumab alone. In the RCT CheckMate 067, 945 treatment-naïve patients were randomly assigned 1:1:1 to receive ipilimumab (3 mg/kg) versus nivolumab (1 mg/kg) versus ipilimumab plus nivolumab (3 mg + 1 mg). Median progression-free survival was superior for ipilimumab plus nivolumab (11.5 months) compared with the nivolumab arm (6.9 months) and the ipilimumab arm (2.9 months; p < .001). In patients with tumors positive for PD-L1, the median progression-free survival was the same (14 months) when treated with nivolumab alone or with the combination. But in patients with PD-L1–negative tumors, progression-free survival was longer for ipilimumab plus nivolumab (11.2 months) compared with nivolumab alone (5.3 months). Combination therapy was the most toxic, with grade 3 or 4 AEs occurring in 55% of those treated with the combination compared with 16.3% for nivolumab and 27.3% for ipilimumab. Overall survival results were reported in 2017. Three-year survival rate for the combination was 58%, 52% for nivolumab, and 34% for ipilimumab. Only the differences with ipilimumab were significant. Patients with 1% or greater expression of PD-L1 did as well with nivolumab alone as with the combination therapy. Only patients with no expression of PD-L1 benefited from the combination. Combination therapy was much more toxic with grade 3 or worse AEs in 59% of those who received it compared with 21% for nivolumab and 28% for ipilimumab. Results from the low-dose ipilimumab (1 mg/kg) in combination with pembrolizumab in advanced-stage melanoma was reported in 2017. With identical efficacy, this combination proved far less toxic, with grade 3 or worse AEs in 27% of patients.

**Other Combination Therapies: Anti–PD-1 Will Be the Backbone**
Immunotherapy combinations in general are expected to be perhaps the most dynamic drug development field for years to come. Once breaking tolerance is achieved, or even further improved with candidate molecules such as anti–LAG3 and others, the door seems wide open to combine with agonists such as OX40, CD137, ICOS-1, and others.

The most prominent combinations under development at the moment are anti–PD-1/PD-L1 with IDO inhibitors and with the oncolytic vaccine T-VEC.

**IDO inhibitors plus anti–PD-1.** The most advanced IDO inhibitor currently in development is epacadostat. In phase I to II studies, 54 evaluable patients with advanced-stage melanoma were treated in combination with pembrolizumab. The overall response rate was 56% (30 of 54 patients; eight complete responses, 22 partial responses), with a 78% disease control rate (complete response + partial response + stable disease). Median progression-free survival was 12.4 months; progression-free survival rates at 6, 12, and 18 months were 70%, 54%, and 50%, respectively.

Similarly, the IDO pathway inhibitor indoximod in combination with pembrolizumab demonstrated excellent activity against advanced melanoma in 51 patients, with an overall response rate of 59%, a complete response rate of 12%, a partial response rate of 47%, and a disease control rate of 80%. These results are not unlike ipilimumab plus nivolumab or pembrolizumab data. The big difference is that epacadostat and indoximod combination therapy are far less toxic, with treatment-related AEs of 3 or higher in only 17% of patients. A phase II RCT of epacadostat with or without pembrolizumab is ongoing, and results are expected in 2018.

**Oncolytic vaccination with T-VEC and anti–PD-1.** Results from a phase IB trial testing the impact of oncolytic virotherapy with T-VEC on cytotoxic T-cell infiltration and the therapeutic efficacy of pembrolizumab indicated very promising activity. In 21 patients treated no dose-limiting toxicities occurred. The ORR was 62%, with a complete response rate of 33%. Patients who responded to combination therapy had increased CD8+ T cells, elevated PD-L1 protein expression,
as well as IFN-γ gene expression on several cell subsets in tumors after T-VEC treatment. Response to combination therapy did not appear to be associated with baseline CD8+ T-cell infiltration or baseline IFN-γ signature. This indicates that T-VEC can turn cold tumors into hot tumors.

Various other combinations can be envisioned. Current developments also focus on radiotherapy and the potential of manipulation the patient’s microbiome.

**RADIATION AND IMMUNOTHERAPY**

There has been extensive preclinical work looking at the interaction of radiation and the immune system, including identifying both the positive effects of radiation with immunotherapy as well as identifying some limiting factors that radiation may have on the efficacy of immunotherapy. On the clinical side, the data have been more limited in nature, with most studies in the phase I/II setting and still awaiting further development of optimal radiation and immunotherapy approaches. To provide a framework for understanding the development and approaches being pursued with radiation and immunotherapy combination, we will discuss known interactions between radiation and immunotherapy as well as discuss specific clinical trials looking at combination approaches and how they inform the future development of the field.

**Radiation and Immunotherapy Interactions**

Combination approaches with radiation have been framed in terms of two distinct interactions: abscopal responses and immune modulation. The first and perhaps more commonly studied is the abscopal response initiated by radiation. In the case of the abscopal response interaction, studies have focused on radiation functioning as an in situ vaccine resulting in the release of both antigen and adjuvant, and when combined with immunotherapy agents results in the enhanced immune control of distant nonirradiated sites of disease.

Although the abscopal response has been described for decades, a recent review of the literature suggests that radiaiton may become integrated earlier in the definitive setting. Preclinical studies looking at abscopal responses following radiation, most studies of radiation and immunotherapy have focused on radiation with checkpoint inhibitors, typically using doses greater than 5 Gy per fraction and have shown synergy with anti–CTLA-4, anti–PD-1, and anti–PD-L1. Some studies have been done with more commonly used 2 Gy per fraction doses and have also shown synergy with anti–PD-L1. Additionally, preclinical studies have shown that radiation can interact to induce systemic immunity when combined with adjuvants including Toll-like receptor ligands, stimulator of interferon genes (known as STING) ligands, costimulatory molecules, and cytokine.

The second radiation and immunotherapy interaction is referred to as immune modulation. In this case, the role of immunotherapy is to enhance the local in-field radiation response through both immune-adaptive and innate-mediated clearance of residual disease. This has not garnered as much interest as the abscopal response but is poised to have a large clinical impact as immunotherapy may become integrated earlier in the definitive setting. This integration of immunotherapeutic agents into the definitive setting may permit radiation treatment modification that may decrease morbidity while enhancing the effect of local radiation therapy. Preclinical studies looking at the efficacy of local radiation in the presence of CD8 depletion have demonstrated a clear CD8-mediated dependence of radiation effect. In addition, retrospective studies in patients have demonstrated that local control with radiation is inferior in immunosuppressed patients. Alternatively, by targeting innate immune cells such as macrophages either by depletion or repolarization, the local effect of radiation can be enhanced. A significant component of immune modulation of the tumor following radiation involves modification of surviving radiated cancer cells, which make them better targets for immune cell–mediated killing by CD8 T cells, natural killer cells, and gamma-delta cells. This includes upregulation of class I, NKG2DL, adhesion molecules such as ICAM, and death receptors including FAS. Typically, upregulation of these markers increases with increasing doses of radiation. Conversely, while the cancer cells upregulate molecules to enhance immune clearance, radiation has also been associated with the upregulation of PD-L1, which may limit this response and allow escape from immune-mediated clearance. Finally, radiation has been associated with an increase in cytokine and chemokine secretion, which results in recruitment of immune cells into the tumor environment; this can occur at even relatively low doses of radiation in the 2-Gy range. Based on the immune modulation effects in the irradiated tumor, there is a strong rationale for bringing a range of immunotherapy agents including PD-1 axis–targeting and TAM-targeting agents into the definitive radiation setting.
Radiation and Immunotherapy Clinical Studies

In terms of clinical trials looking at the combination of radiation and immunotherapy agents, studies have been reporting on the combination since the early 1990s, but almost all of these have been single-arm studies that limit the ability to comment on the efficacy of these combinations. Studies are actively ongoing that randomly assign patients to receive radiation plus immunotherapy alone, and, in the next few years, we may have some answers as to whether radiation adds anything to immunotherapy for the treatment of metastatic cancer. Several combination studies warrant specific discussion. The most extensively reported combination includes several studies with radiation and ipilimumab. The largest study in metastatic castration-resistant prostate cancer looked at radiation 8 Gy × 1 to a bone metastasis followed by either ipilimumab or placebo. There was no significant difference in median OS between patients receiving ipilimumab compared with placebo, and it is unclear if responses were higher than would be expected if ipilimumab was given without radiation.75 Subsequent single-arm studies of radiation with ipilimumab have been reported. Two studies looked at patients with metastatic melanoma treated with radiation and ipilimumab. The first reported on 22 patients with metastatic melanoma treated to a single-index lesion with 6 to 8 Gy per fraction in 2 to 3 fractions followed by four cycles of ipilimumab. The response rate was reported at 18% partial responses with no complete responses. Median OS was 10.7 months.76 The second prospective study in metastatic melanoma again treated 22 patients with radiation delivered to one to two sites of disease within 5 days of starting ipilimumab. The radiation dose in this study was extremely heterogeneous, but they reported a 27% overall response rate with a 13% complete response rate. The median OS in this study was 12.5 months.77 Although both of these studies report higher overall responses of 18% to 27% compared with the pivotal ipilimumab study,1 which reported a 10.9% overall response, this is comparable with the more recent 19% overall response rate reported in the recently published results on the combination of nivolumab and ipilimumab.44 Finally Tang et al reported on a phase I trial of ipilimumab in solid cancers treated in combination with radiation given at doses of 12.5 Gy × 4. A total of 31 patients were treated; the overall response rate was 10% and median OS was 10 months.78 It is difficult to make comparisons with this final study to historic controls as a variety of solid tumors were treated, but it should be noted that there was only one patient with melanoma (uveal subtype). Nonetheless, to date, the single-arm studies published investigating the combination of radiation and CTLA-4 inhibition are not holding to the promise that the preclinical studies and case reports seemed to imply.

There are a number of additional radiation and checkpoint inhibitor studies that are actively accruing and include combinations with PD-1–axis inhibition that will likely be reporting in the next few years.79 There is one phase I study of radiation in combination with pembrolizumab in patients with metastatic solid tumors that has recently been published. In this study, patients typically received radiation to two sites of disease followed by initiation of pembrolizumab within 7 days of radiation. The reported overall objective response rate was 13.2%, and it is difficult to know if this is better than expected with pembrolizumab alone as it included a variety of solid tumors.80

Finally, there have been a number of studies published looking at radiation in combination with high-dose interleukin-2 (IL-2). Of particular interest is that each of these studies used high-dose IL-2, but radiation was given with distinct dose regimens in each study. The first study, reported in 1991, looked at 5 Gy per fraction of radiation given in 2 to 4 fractions followed by high dose IL-2 in patients with metastatic melanoma. This study treated 28 patients and reported a response rate of 7%, which was no better than comparable high-dose IL-2 alone.81 The second study was in patients with metastatic renal cell carcinoma and included 16 patients treated with a single 8 Gy fraction given before cycle 1 and 2 of high-dose IL-2. In this case, they reported an overall response rate of 12%, and this was again considered comparable to rates seen with high-dose IL-2.82 The final study, reported in 2012, included 12 patients with metastatic melanoma and renal cell carcinoma who received 20 Gy × 1 to 3 fractions and reported an overall response rate of 66.6%.83 This was considerably higher than response rates typically seen with high-dose IL-2 alone. The obvious difference between these three studies is the significantly higher dose per fraction of 20 Gy compared with 5 to 8 Gy used in the earlier studies. A randomized phase II study in melanoma comparing this high-dose radiation plus IL-2 compared with IL-2 alone has completed accrual and will report data to determine if the response rate holds out in a larger study.

Finally, the recently reported PACIFIC trial in non–small cell lung cancer has brought immune checkpoints into the locally advanced, rather than purely metastatic, setting and has shown a substantial improvement in progression-free survival in patients receiving adjuvant PD-L1 inhibition following definitive chemoradiation compared with chemoradiation alone.84 This may serve as the starting point for combining immunotherapy with radiation in the definitive setting.

The preclinical combination of radiation and immunotherapy has shown very promising interactions. The early clinical studies have been relatively mixed. There remains a significant amount of work needed to identify which immunology agents are best in combination and how best to deliver the radiation to optimize immune responses.

IMMUNOTHERAPY AND THE MICROBIOME

Living organisms are constantly interacting with the environment, and these interactions can shape immune responses and even responses to immunotherapy. A clear example of this involves the microbiome. The microbiome refers to the collective genomes of microbes within a given community, consisting of multiple different microbiota including bacteria, viruses, fungi, and protozoa. Within a living person, hundreds of trillions of microbiota are found over several
different anatomic sites, with a large proportion of these present in the gastrointestinal tract. Over the past several years, significant evidence has emerged regarding the impact of the microbiome on overall health, as well as several disease states including cancer. In addition to this, there is now clear evidence that the microbiome can influence response and toxicity to cancer immunotherapy, with strategies targeting the microbiome under development to try to augment responses and abrogate toxicity to cancer immunotherapy.

**The Gut Microbiome Shapes Host Immunity**

There is substantial interaction between the gut microbiome and the host, with a surface area between 30 and 40 m² in the gut of the average human. Microbiota are present at every level of the gastrointestinal tract, though the amount and composition at different sites varies considerably. The microbiota are known to play a critical role with host digestion and energy balance, and the immune system has evolved to allow tolerance to these critical commensal microbiota while protecting the host against intestinal pathogens. Several factors influence this critical balance, including a mucus layer as well as production of antimicrobial peptides and immunoglobulins. The lamina propria of the gut contains an extensive network of immune cells along the entire length of the gut that facilitate tolerance to commensal bacteria as well as food antigens. This is accomplished at the local level via the recognition of bacterial proteins by receptors such as Toll-like receptors, which induce maturation of dendritic cells that may then migrate to mesenteric lymph nodes inducing specific T-cell subsets such as regulatory T cells, which then traffic back to the gut and mediate tolerance via the production of immunosuppressive cytokines and other means. However, it is now quite evident that immune cells educated within the gut may circulate systemically, thus shaping overall immunity.

Evidence regarding the impact of the gut microbiome on immunity at and beyond the level of the gut is demonstrated in preclinical models, as well as in human cohorts. Germ-free mice that lack commensal bacteria in the gut demonstrate profound defects in cellular and humoral immunity at the level of the gut and also exhibit markedly impaired systemic immune responses. Studies in human cohorts show that the diversity and composition of the gut microbiome may influence immune responses such as those to vaccination, with enhanced vaccine responses observed in individuals with a higher diversity of the gut microbiome. Compositional differences in the gut microbiome may also influence responses to vaccination. Interestingly, defects in the gut microbiome may also potentially influence cancer immunosurveillance, highlighted by a study demonstrating that chronic antibiotic use (which is known to negatively impact the gut microbiome) is associated with a higher risk of colonic adenomas.

**Characterizing the Gut Microbiome**

Characterization of the gut microbiome has been greatly facilitated by the application of next-generation sequencing techniques. While methods (as well as reference genomes for comparison) are still being refined, several metrics to characterize the microbiome are commonly applied.

Perhaps the most common means of assessing the diversity and composition of the gut microbiome involves sequencing of ribosomal 16S rRNA, which is present in prokaryotic cells but not in eukaryotic cells. Within the 16S gene, there are nine hypervariable regions that can be assessed and used to discriminate different bacterial taxa. The most commonly sequenced of these variable regions include V3, V4, and V6. Reads derived from sequencing are then matched to reference genomes such as SILVA or Greengenes, leading to the identification of bacterial operational taxonomic units and quantification of diversity.

Diversity is a common metric and assesses the distribution and assembly patterns of microbial communities. Alpha diversity reflects the diversity of bacterial operational taxonomic units within a given sample and is most commonly expressed via ecologic indices such as Shannon or Inverse Simpson i. Beta diversity reflects the intersample diversity between different samples and can be interpreted as the degree of similarity (or lack thereof) between sample groups. Compositional differences may also be described by evaluating the differential abundance of operational taxonomic units between populations. Linear discriminate analysis of effect size is one tool commonly used to compare and visualize the effects sizes associated with compositional differences between groups.

In addition to 16S sequencing, whole-metagenomic shotgun sequencing is used and offers some distinct advantages over 16S methods. As opposed to sequencing one amplicon, the entire bacterial genome is sheared, sequenced, and subsequently mapped against reference databases. In addition to gaining greater resolution of bacterial taxa to the species level, whole-metagenomic shotgun sequencing allows for mapping against metabolic pathway databases for insight into the function of the constituent bacterial communities. Although the cost of whole-metagenomic shotgun sequencing is currently significantly higher than that of 16S sequencing, it is declining with more widespread use and is predicted to be the dominant sequencing method in the near future.

**The Microbiome and Response to Immunotherapy**

Preclinical studies demonstrating an impact of the gut microbiome on response to cancer immunotherapy date back over a decade, though the most provocative evidence was published in Science in 2015, which showed an impact of compositional differences in the gut microbiome to the immune checkpoint blockade targeting CTLA-4 or PD-1. These provocative studies spurred tremendous interest and a desire to validate this in human cohorts, and several studies have now been published demonstrating differential “signatures” in the gut microbiome of responders compared with nonresponders to immune checkpoint blockade, with a higher diversity of bacteria in the gut microbiome of responders versus nonresponders as well as compositional differences.
with a higher abundance of bacteria such as Akkermansia, Faecalibacterium, Bifidobacterium, and Ruminococcaceae (among others) in responders compared with nonresponders.\textsuperscript{97,99,117,118} Importantly, this observation was made across cancer types in the setting of treatment with immune checkpoint blockade, suggesting that this is not unique to melanoma. Differences did exist across the cohorts with regard to specific bacterial taxa associated with response or resistance, however, different techniques for sequencing and analysis were used. Additional studies are needed to validate these findings and to better understand the unifying and distinguishing features among these cohorts and factors accounting for differences (such as geography and diet).

Despite some limitations, important insights were gained through these studies. Mechanistic studies were performed in these cohorts in correlative studies in tumor biopsies and in parallel murine models, suggesting a clear link between a “favorable” gut microbiome and enhanced antitumor immune responses.\textsuperscript{97,98} In addition, one of these studies elegantly demonstrated that patients who received antibiotics just prior to or just after the initiation of immune checkpoint blockade had significantly lower survival,\textsuperscript{98} suggesting that disruption of the gut microbiome can impair antitumor immunity. These studies also highlight the potential utility of the gut microbiome as a biomarker of response, as this was quite a strong predictive factor to response to anti–PD-1 therapy in several of these studies.\textsuperscript{97,99} However, whether this is predictive or prognostic is still in question and begs further investigation.

Perhaps the most profound finding in these studies was the observation that fecal microbiome transplantation from patients with responding versus nonresponding disease into germ-free mice could recapitulate the phenotype observed in patients, with delayed tumor outgrowth and enhanced responses to immune checkpoint blockade in germ-free mice receiving responding versus nonresponding fecal microbiome transplantation.\textsuperscript{97,99} Furthermore, modulation of the gut microbiome in these studies was associated with enhanced responses to immune checkpoint blockade,\textsuperscript{97,99} providing the foundation for future studies in clinical trials.

The Microbiome and Immunotherapy Toxicity

In addition to influencing therapeutic response, the gut microbiome has also been shown to influence toxicity to immunotherapy. Early studies in patients undergoing hematopoietic stem cell transplant demonstrated that patients who developed graft versus host disease had a much lower diversity of bacteria in the gut microbiome and a markedly lower abundance of bacterial taxa associated with overall gut health, such as Ruminococcus, Lactobacillus, Faecalibacterium, and Blautia.\textsuperscript{119-122} Cohorts of patients with or without toxicity on immune checkpoint blockade have recently been studied, revealing that patients who failed to develop CTLA-4–associated colitis had a higher abundance of bacteria in the Bacteroidetes group within their gut microbiome,\textsuperscript{122} potentially via modulation of regulatory T cells within the colonic mucosa. These findings certainly suggest a role for the gut microbiome in mediating therapeutic toxicity, however, this must be studied in larger cohorts.

Manipulating the Microbiome as an Adjunct to Immunotherapy

Based on this growing body of evidence, there is now a great deal of enthusiasm to manipulate the microbiome as an adjunct to immunotherapy. The concept of modulating the microbiome in the treatment of disease is not new, and approaches such as these are being used to treat conditions outside of cancer, ranging from ulcerative colitis to Parkinson disease.\textsuperscript{124,125}

Nonetheless, there exists a range of options for modulating the microbiome, and ideal methods have not yet been defined in the treatment of cancer. Dietary interventions have been proposed, and there are ongoing studies evaluating the impact of changes in diet on the microbiome and other parameters in patients with cancer (NCT02843425). These early studies do not include response assessment as an endpoint, and such studies must be developed if we are able to demonstrate that dietary changes can indeed have a profound impact on the gut microbiome in this patient population.

Other methods exist and are being actively pursued, including fecal microbiome transplantation from complete responders, to anti–PD-1 therapy (NCT03353402), to a group of patients with refractory disease. Additional studies aim to evaluate the administration of defined bacterial consortia and fecal microbiome transplantation are also in development, though it is currently not clear from published literature what an ideal consortia of bacteria contains. Monoclonal microbial preparations are also being considered based on preclinical and clinical findings.\textsuperscript{126}

Certainly strategies like these are key to consider in this age of precision cancer medicine and in light of the impact of the microbiome, though we must exercise great care as we move forward and must work together to provide optimal benefit to our patients.

References


GASTROINTESTINAL (COLORECTAL) CANCER
An estimated 140,250 Americans will be diagnosed with colorectal cancer (CRC) in 2018. Of these, approximately 20% will present with de novo metastatic disease, and among those presenting with earlier-stage disease treated with resection, another 35% will relapse with distant metastatic disease after an initial disease-free interval. For the estimated 30% to 5% of patients with liver-limited or oligometastatic disease, it has long been recognized that surgical metastasectomy may achieve durable disease control and potentially cure. However, less than 10% of patients with metastatic CRC (mCRC) present with upfront resectable disease. Consequently, to achieve the goal of converting potentially resectable metastatic disease to resectability requires a multidisciplinary approach, including medical and surgical oncologists and, increasingly, radiation oncologists and interventional radiologists. Herein, we summarize recent developments in systemic therapy, radiotherapy, and interventional liver-directed therapies that have changed the treatment landscape for patients with oligometastatic colorectal cancer.

Beyond the Knife: The Evolving Nonsurgical Management of Oligometastatic Colorectal Cancer
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OVERVIEW

In patients with liver-limited oligometastatic disease, the goal of treatment can be curative intent. Historically, this was accomplished in patients presenting with upfront resectable disease. The availability of increasingly efficacious chemotherapy and biologic combinations with encouraging response rates led to the potential to convert unresectable disease to resectability. Beyond the backbone of surgery, we now have a portfolio of locoregional strategies to consider. From an interventional radiology perspective, the use of portal vein embolization can facilitate hypertrophy of the liver in anticipation of resection, thus converting unresectable disease to one amenable to a surgical approach with curative intent. Technological advances in liver-directed ablative therapies have afforded the possibility of eliminate radiographically evident disease with the hope for long-term disease control. Advanced radiotherapy techniques are further increasing the therapeutic options for patients with metastatic colorectal cancer. Improvements in external-beam radiotherapy over the past 2 decades include image-guided radiotherapy, intensity-modulated radiotherapy, stereotactic body radiotherapy, and proton-beam therapy. Finally, selective internal radiation therapy (SIRT) with microspheres labeled with the β-emitter $^{90}Y$ enable targeted delivery of radiation to hepatic tumors. A coordinated multidisciplinary approach is required to integrate these nonsurgical adjuncts in an evidence-based manner to optimize outcomes for patients with potentially resectable metastatic disease. In this article, we summarize recent developments in systemic therapy, radiotherapy, and interventional liver-directed therapies that have changed the treatment landscape for patients with oligometastatic colorectal cancer.

SYSTEMIC THERAPY FOR CONVERSION: WHEN RESPONSE RATE IS THE GOAL

Choice of Chemotherapy Backbone

The choice of chemotherapy regimen is dictated by several factors, including efficacy, tumor RAS status, toxicity, cost, and patient preference. Ultimately, however, when the intent is to convert potentially resectable disease to a complete R0 resection, the primary metric of efficacy is typically response rate. For patients with good performance status, combination chemotherapy regimens with 5-fluorouracil and oxaliplatin (FOLFOX), irinotecan (FOLFIRI), or both (FOLFOXIRI) are all reasonable considerations. Because of the concern for irinotecan-related steatohepatitis, FOLFOX is commonly preferred; however, FOLFIRI remains an option, particularly in patients who have recently received FOLFOX in the adjuvant setting.

Objective response rates of 45% to 55% were demonstrated with the doublet regimens in the prebiologic era. Trials comparing the triplet regimen of FOLFOXIRI to FOLFIRI demonstrated significantly higher response rates (60% vs. 34%; p < .0001) with higher rates of secondary liver resection among patients with initially unresectable disease (15% vs. 6%).

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Role of Biologics

With respect to biologics, the benefit of the VEGF monoclonal antibody bevacizumab in potentially resectable disease, with a goal of maximizing response rates, is still uncertain. In randomized trials, the addition of bevacizumab to oxaliplatin-containing chemotherapy did not meaningfully improve response rates; whereas a modest response rate improve was observed with irinotecan and 5-fluorouracil in combination with bevacizumab when administered as the IFL regimen. In the context of triplet therapy, the TRIBE trial of bevacizumab with FOLFOXIRI demonstrated a response rate of 65%, similar to that previously reported with FOLFOXIRI alone. Beyond the questionable incremental improvement in response rates with bevacizumab, the concerns regarding operative toxicity with respect to bleeding, impaired wound healing, and impaired hepatic regeneration remain despite conflicting evidence. As a consequence, it is recommended that bevacizumab be withheld for 6 to 8 weeks before resection, recognizing the 3-week half-life of this agent.

The incremental improvement in response rates with EGFR monoclonal antibodies—cetuximab and panitumumab—is somewhat compelling in the 40% of patients with mCRC who have RAS wild-type (WT) disease; however, this is also not without controversy. The phase II CELIM trial of cetuximab with FOLFOX or FOLFIRI demonstrated response rates of 57% to 68% with a 38% R0 resection rate. In another randomized trial from China, a response rate of 57% was reported with doublet chemotherapy plus cetuximab versus 29% with chemotherapy alone. However, the new EPOC trial of FOLFIRI with or without cetuximab in the peri-metastasectomy setting showed a significantly detrimental impact on progression-free survival with the addition of cetuximab (HR 1.48; p = .030). Although this study was in the upfront resectable setting, it raises concerns regarding the application of an EGFR-containing regimen in patients who may be proceeding to a hepatic resection.

Another important consideration is the duration of therapy in patients for whom resectability is the goal. Because best response is typically observed within the first six to eight cycles of treatment, if sufficient response to be considered for resection has not been achieved within 4 months of therapy, the likelihood of achieving resectability with continued therapy is low. Recognizing that treatment-related toxicity, particularly hepatotoxicity, is correlated with number of administered cycles, it is equally important to recognize that systemic therapy should continue to resectability and not necessarily to maximal response. Thus, close coordination between the medical oncologist and the surgical and interventional oncologists is imperative.

INTERVENTIONAL RADIOLOGY: THE DRIVE TO SURGICAL RESECTION OR CURATIVE INTENT

Portal Vein Embolization

The liver demonstrates unique regenerative abilities because of its histopathologic and functional architecture. In brief, liver perfusion is based on inflow of hepatic arterial flow and portal venous flow. The organ itself is organized in parallel functional units (hepatic lobules) and demonstrates the ability to rapidly proliferate and regenerate in the setting of acute injury/insult. As a result of this condition, a large fraction of liver tissue may be resected in anticipation of hepatic regeneration. However, there are limitations to the compensation response. In liver with no compromise to hepatic reserve (no chemotherapy, noncirrhotic, no portal hypertension), up to 80% of the liver may be resected with extremely low incidence of hepatic failure. In the setting of compromise to hepatic reserve, up to 60% of the liver may be resected with a slightly higher incidence of hepatic failure.

In patients presenting with high-volume liver nonresectable metastatic disease, two options exist to facilitate conversion to surgical resectability: (1) tumor downsizing through systemic or locoregional therapy and (2) hypertrophy of the remaining liver. The decision to pursue these strategies in isolation or in combination largely depends on review in a multidisciplinary setting, drawing from the expertise of the medical oncologist, surgical oncologist, radiologist, and interventional radiologist. Techniques have been developed to facilitate hypertrophy of the liver in anticipation of surgical resection, thus converting...
potential nonresectability to curative intent. The use of portal vein embolization is predicated on knowledge that aggressive surgical ligation of the portal vein resulted in a clinically measurable compensator hypertrophic response in the remaining liver. Diversion of blood flow (causing increased hydrostatic pressure and transient portal hypertension), as well as increased expression of hepatotrophic mediators, has been theorized to facilitate the hypertrophic change in the residual liver, facilitating conversion of patients whose disease may not be surgically resectable to those with resectable disease.\(^{16}\)

Various techniques have been described with respect to portal vein embolization, but the general principle is based on minimally invasive image-guided techniques. The general approach is summarized as follows: Percutaneous portal venous access is obtained through the liver under ultrasonographic or fluoroscopic guidance. Following this, selective catheterization of the individual branches of the portal vein within the liver volume that is intended for surgical resection is selectively embolized with particles, coils, liquid embolics (glue), or combinations of such, to divert portal venous flow into the portion of liver that is intended to remain, as well as increased expression of hyperproliferation factors secondary to the insult to the portion of liver that is intended for surgical resection.

Follow-up CT, typically 6 weeks, is performed to measure the degree of relative hypertrophy of the future liver remnant and overall total liver volume with anticipation of surgical resection if appropriate hypertrophy occurs. Hypertrophic changes then typically occur immediately and reach their nadir at 4 to 6 weeks, at which time reassessment for resectability based on the future liver remnant growth will be conducted. Changes in future liver remnant as high as 81% ± 47% have been reported by using various embolic materials;\(^ {17}\) the general consensus is that microspheres or cyanoacrylate results in increased growth.\(^ {18}\) Postsurgical survival is reported to be equivalent or superior to that among those patients undergoing surgical resection alone (5-year survival, 44% vs. 35%, with a statistically significant difference of 56.9% versus 8.9% (HR 0.58; 95% CI, 0.38–0.88; p < .01).\(^ {19}\) This situation may be explained through the delay in surgery, as well as increased expression of hyperproliferation factors that may not be receiptable to those with resectable disease.\(^ {20}\)

In summary, portal vein embolization is intended to extend the resection margins and optimize the function of the remaining remnant, lowering the potential for liver failure. Aggressive and creative approaches can be developed to remove all visible disease through this adjunct procedure, but they require thoughtful review of the imaging by both surgeon and interventional radiologist in the setting of a multidisciplinary team.\(^ {21}\)

**Ablation Strategies**

The prognosis in patients with colorectal liver metastasis is largely determined by the degree of liver tumor infiltration. The rationale and use of liver-directed therapies for the treatment of resectable disease, or potentially locally curative therapy through surgical resection, have been established with both long-term population-based outcomes and smaller randomized control trials despite high rates of recurrence within the liver.\(^ {20,21}\)

Various energy-based ablative platforms are available (cryoablation, microwave ablation, irreversible electroporation), with most of the published literature relating to radiofrequency ablation. A discussion relating to the technology platforms is beyond the scope of this article, and interested readers may refer to review articles specific to the topic. Clinically, radiofrequency ablation is widely considered the most mature in terms of both technology and publication, and it remains the standard by which new ablative therapies (including stereotactic radiotherapy [SBRT]) are measured.\(^ {22}\)

Although the acceptance of hepatic resection and conversion to resectability have become mainstream, discussion and research on curative intent ablative therapies largely entail single-arm studies that often are retrospective. Furthermore, the high rate of recurrence of liver metastasis in patients undergoing curative intent questions the utility of aggressive surgical resection in the setting of small tumor burden. Because of the high variability in patient selection, randomized controlled trials comparing surgical resection to curative intent ablation have been limited.\(^ {23}\)

As a result of the variations in morphology, technique, and technologies, 5-year survival benefit has been used as a primary measure of efficacy, based on the low rates seen (145-year survival rate of 14% in patients with distant spread of disease, most hepatic) with optimized chemotherapeutic and biologic regimens.\(^ {24}\)

Many articles have reported outcomes with the incorporation of radiofrequency ablation into clinical practice. However, the variability of application (e.g., oligometastatic disease with curative intent, extension of irradiation of tumors that cannot be resected as an adjunct to resection, treatment upon recurrence, neoadjuvant setting) result in high variability in patient selection. Table 1 outlines the more commonly cited literature.\(^ {25–35}\)

Two studies (by Kim and colleagues\(^ {36}\) and Ruers and colleagues\(^ {30}\)) provide some perspective on the indications and efficacy of ablation in the setting of colorectal liver metastasis. Kim and colleagues retrospectively reported on a subset of patients presenting with solitary colorectal liver metastasis of less than 3 cm, comparing surgical resection to radiofrequency ablation with curative intent. In the subset of patients who met these criteria, no significant difference was observed with respect to disease-free survival and overall survival (p = .962) between patients undergoing surgical resection and those receiving radiofrequency ablation.\(^ {36}\)

Ruers and colleagues’ recent publication of the CLOCC data set (EORTC Intergroup phase II study [EORTC 40004]), examining a strategy of colorectal liver metastasis eradication through a surgical resection/ablation approach, had demonstrated a significant improvement in all clinically relevant parameters, highlighted by an 8-year overall survival rate of 56.9% versus 8.9% (HR 0.58; 95% CI, 0.38–0.88; p < .01) comparing radiofrequency ablation plus chemotherapy...
versus chemotherapy alone. One may infer from this landmark study that curative-intent locoregional therapies result in improvement in survival and greater control of progression compared with systemic therapy alone.

With these two studies, two emerging roles for ablation become apparent: (1) in patients with low-volume disease amenable to curative ablation as opposed to surgical resection due to the expected high rates of recurrence and (2) in patients presenting with a high burden of disease that is nonresectable, even with conversion therapy that may involve ablation only, or as a combinatorial approach to eradication of all identifiable tumor burden.

The technical limitations of radiofrequency ablation in lesions less than 3 cm (near vascular structures, subcapsular, central) may be overcome by microwave ablation, cryoablation and irreversible electroporation. However, controversy remains as to whether patients presenting with lesions less than 3-cm benefit from ablation, despite newer technologies allowing for larger ablation zones, as the biology of patients with large tumors (not necessarily large burden of disease) has not been clearly established.

In summary, incorporation of an ablation strategy is an essential component of multispecialty care in the patient diagnosed with colorectal liver metastasis. The technologies and techniques have advanced substantially, with a greater emphasis on larger ablations and efficiency predicted on the justifiable assumption that removal of radiographically visible disease translates into a survival benefit.

**Embolization**

The fundamental concept of hepatic arterial embolic therapy is based on the process of tumor angiogenesis and the exploitation of the vascular capacitance of the tumor to administer high concentrations of chemotherapy loaded on calibrated microparticles through a process of ionic binding. Delivery of the chemotherapy is based on plasma ion exchange as a function of time, resulting in sustained concentrated locoregional delivery of the chemotherapeutic agent. Through the compartmentalization of chemotherapy, decreased toxicities, increased concentrations, and potentially improved tumor response may occur, in hopes of altering or regulating tumor biology, translating into an improvement in survival. Most commonly, irinotecan is used as the systemic therapeutic agent in the treatment of mCRC, so termed DEBIRI.

The current body of literature relating to the use of DEBIRI has been limited by risk of bias and the strength of reported results. A comprehensive critical review of the use of this technique, including elution profile of the various microsphere manufacturers, particle size, and chemotherapeutic...
intensity, concluded that the small body evidence (primarily restricted to small retrospective analyses, and phase IIa observational prospective studies) limited broad adoption of DEBIRI.38

Recently, Martin and colleagues reported on the largest randomized controlled trial to date of patients undergoing DEBIRI.39 They recruited 70 patients into this two-group study to compare FOLFOX6 and bevacizumab versus mFOLFOX6 and DEBIRI with or without bevacizumab in the first-line setting. The primary endpoint was response rate. The overall response rate was significantly greater in the interventional arm at 2 months (70% versus 54%; p = .02) and at 6 months (76% versus 60%; p = .05), achieving success in the primary endpoint.39

However, critics have stated concern regarding the introduction of additional chemotherapeutic agents in the experimental arm, questioning whether the reported improvement in outcome may be confounded by the systemic effects rather than the liver-directed therapy. Under these pretenses, a proper study would be best compared with a FOLFOXIRI/FOLFIRINOX regimen as opposed to what is being described in the study, which is FOLFOX alone. The authors concluded that the simultaneous administration of microspheres is safe and does not cause treatment delays or increase systemic toxicity of chemotherapy, with the added benefit of improved overall response rate, improved hepatic progression-free survival, and more durable overall progression-free survival (with a statistically increased incidence of downslope to surgical resection). Given the limited evidence, the use of DEBIRI should be reserved for further study.

RADIOThERAPY FOR OLIGOMETASTASES: ADVANCES IN EXTERNAL BEAM AND SELECTIVE-INTERNAL RADIATION

Modern advanced radiotherapy techniques are increasing the therapeutic options for patients with oligometastatic mCRC. Improvements in external-beam radiotherapy (EBRT) over the past 2 decades include image-guided radiotherapy, intensity-modulated radiotherapy, SBRT, and proton-beam therapy.

Although the standard dose for primary rectal cancer is generally 45 to 54 Gy in 1.8-Gy fractions daily, some investigators report that hepatic metastases from CRC are more radioresistant than other liver metastases clinically.40,42 SBRT can potentially allow delivery of higher biologic doses of radiotherapy than conventional fractionation in three to five fractions over 2 weeks, with greater convenience for patients and potentially higher efficacy than conventional radiotherapy. It requires very accurate image guidance and motion management to ensure a high degree of spatial accuracy. At most centers, SBRT is generally offered to patients with up to three to five liver metastases and small treatment volumes (< 8 cm lesion diameter), but it can be used to treat more lesions depending on their locations within the liver and larger tumors as long as sufficient normal functioning liver (700 mL minimum) can be spared.42,43 Larger lesions are commonly treated with three-dimensional conformal radiotherapy or intensity-modulated radiotherapy with 45 to 66 Gy in 1.8-Gy fractions.44

For all forms of external-beam radiotherapy to the liver, it is recommended that patients have high-quality triphasic CT planning scans, ideally with coregistration of MRI, with or without positron-emission tomography for accurate target delineation.42,44 Because the liver moves with breathing, techniques for motion management are essential, as is image-guided radiotherapy, such as cone-beam CT with or without radio-opaque fiducial markers.45,46 Techniques used by liver centers include abdominal compression, measured breath-hold, and gated-radiotherapy treatment during the breathing cycle.45,46 If four-dimensional CT is used, an internal target volume is defined to encompass the target volume in all respiratory phases.43

Many studies have evaluated the safety, feasibility, and toxicity profile of SBRT in the management of hepatic tumors.36,47-50 Particular caution must be exercised regarding the proximity of adjacent luminal gastrointestinal structures because all forms of EBRT can cause hemorrhagic gastritis with doses greater than 7 Gy to one third of the stomach51 or colonic/duodenal ulceration with doses greater than 30 Gy in three fractions.52 Departmental protocols are based on international guidance51; if substantial compromise of the planning target volume is likely to be required, the treating oncologist may decide to change to conventional fractionation.

Radiation-induced liver disease (RILD) has been the main limiting factor for the use of EBRT in hepatic tumors. RILD is characterized by central sinusoid congestion with adjacent hepatic atrophy54 and usually occurs from a few weeks to 4 months after irradiation. Traditionally, a 5% risk for RILD after 32 Gy to the whole liver at 2 Gy per fraction is quoted.55 The risk for RILD is considered proportional to the mean dose of radiation to the normal tissue as the liver follows the parallel architecture model of radiobiology.48 By sparing sufficient functioning liver, doses up to 90 Gy have been reported to be safely given to up to a third of the liver volume.42,56,57 From the patient’s perspective, nausea, elevated liver enzymes, acute skin erythema, asthenia, thrombocytopenia, and chest wall pain have been observed following EBRT.

Various studies have shown promising local control rates after SBRT as a focal treatment of CRC oligometastases in multiple organs, including liver, lung, and lymph nodes.52,58-60 Some studies have included hepatic oligometastases from multiple primaries, including CRC.43,47,61-69 Studies that included only inoperable hepatic oligometastases from CRC are listed in Table 2.36,48,50,70,71 Of note, rates of Common Terminology Criteria for Adverse Events (CTCAE) adverse events of grade 3 or greater toxicity range between 0% and 15% in the six studies listed in Table 1, confirming that SBRT is generally well tolerated.

Local control rates at 1 year for SBRT from three prospective and three retrospective studies of treatment for CRC hepatic metastases range between 50% and 100%, and overall
<table>
<thead>
<tr>
<th>Study (Year), Type</th>
<th>No. of Patients</th>
<th>Lesions</th>
<th>Dose/Fraction, Gy</th>
<th>BED</th>
<th>Size, mm</th>
<th>Median Follow-up (Months)</th>
<th>Local Control at 1 Year (%)</th>
<th>Local Control at 2 Years (%)</th>
<th>Overall Survival at 1 Year (%)</th>
<th>Overall Survival at 2 Years (%)</th>
<th>Median Progression-Free Survival (Months)</th>
<th>Toxicity ≥ CTCAE Grade 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van der Pool et al (2010), phase I/II</td>
<td>20</td>
<td>31</td>
<td>37.5–45/3 #</td>
<td>–</td>
<td>7–60 (median, 23)</td>
<td>26</td>
<td>100</td>
<td>74</td>
<td>100</td>
<td>83</td>
<td>11</td>
<td>15 (2 hepatic events)</td>
</tr>
<tr>
<td>Chang et al (2011), phase I</td>
<td>65</td>
<td>102</td>
<td>22–60/1–6 #</td>
<td>40.5–180 Gy</td>
<td>30 mL</td>
<td>14.4</td>
<td>67 84 (≥ 42 Gy)</td>
<td>55 66 (≥ 42 Gy)</td>
<td>72</td>
<td>38</td>
<td>–</td>
<td>6 (2 hepatic, 2 gastrointestinal events)</td>
</tr>
<tr>
<td>Doi et al (2017), retrospective</td>
<td>24</td>
<td>39</td>
<td>45–72 in 4–33 #</td>
<td>71.7–115.5 Gy</td>
<td>≤ 30</td>
<td>30–50</td>
<td>&gt; 50</td>
<td>16</td>
<td>67.2</td>
<td>35.9</td>
<td>81.3</td>
<td>67.1</td>
</tr>
<tr>
<td>Joo et al (2017), retrospective</td>
<td>70</td>
<td>103</td>
<td>45–60 in 3–4 #</td>
<td>60–180 Gy</td>
<td>&lt; 30</td>
<td>≥ 30</td>
<td>34.2</td>
<td>93</td>
<td>73</td>
<td>75</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>McPartlin et al (2017), phase I and II</td>
<td>60</td>
<td>105</td>
<td>22.7–62.1 in 6 # over 2 weeks</td>
<td>–</td>
<td>6–21</td>
<td>28.1</td>
<td>49.8</td>
<td>32 (26 at 4 years)</td>
<td>63</td>
<td>26 (9 at 4 years)</td>
<td>16.0</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Abbreviations: BED, biologically effective dose; CTCAE, Common Terminology Criteria for Adverse Events.

Studies including stereotactic radiotherapy cases for liver metastases from primary cancers other than colorectal cancer are not listed in this table.
survival rates at 2 years range between 26% and 83%. However, out-of-field recurrences are common, with rates reported between 59% and 68%. Patient selection is therefore important; preferably, patients should be selected for SBRT if they seem less likely to develop other metastases in the near future, without or with the addition of systemic therapy. Clinical trials exploring this approach include those combining SBRT for mCRC with immunotherapy.

A pooled analysis of 47 patients evaluated a range of doses between 22 and 60 Gy and showed that total dose, dose per fraction, and biologically effective dose (BED) correlated with local control (p = .06). The best-fit curve estimated that a dose of 48 Gy or greater in three fractions (BED, 117 Gy) was required for a 1-year local control rate of greater than 90%. In a separate study, a retrospective analysis of 70 patients showed that more prolonged local control was observed if higher doses were used; the optimal BED dose was greater than 132 Gy. The 2-year local control rate for lesions receiving BED at greater than 132 Gy was 89%; for those receiving 100 to 112 Gy and 60 to 80 Gy, the rates were 83% and 52%, respectively. The optimal dosimetric parameters for an effective ablative dose with minimal toxicity require further evaluation through clinical trials.

Proton-beam therapy uses charged particles to deposit dose at a defined depth with a very sharp fall-off in dose, potentially reducing irradiation of the surrounding normal tissue. One prospective phase II study of 89 patients with hepatic metastases, of varying histologic types (34 CRCs), used protons to doses of 30 to 50 gray equivalents in five fractions (BED, 48–100 Gy; relative biologic effectiveness, 1.1) and had a median follow up of 30.1 months. There were no CTCAE grade 3 or greater toxicities, and 1- and 2-year local control rates were 71.9% and 61.2%, respectively. Interestingly, as suggested by other investigators using SBRT with photons, CRC metastases in the photon-beam therapy study had worse local control than did other tumors.

Somatic analyses showed that tumors with mutant KRAS and TP53 tumors were more radioresistant than tumors wild-type for the same genes, and that mutation of the KRAS oncogene was a strong predictor of poor local control. This study is an important demonstration that proton-beam therapy safe and effective to treat oligometastases from mCRC.

In practice, SBRT is usually the second choice if surgical resection is not feasible. One study evaluated the outcomes of patients with pulmonary oligometastases after SBRT with those after pulmonary metastasectomy. Despite the selection bias (SBRT was second choice in this study if resection was not possible), 2-year local control rates did not significantly differ between the two study groups: 94% for SBRT and 90% for resection.

Despite its widespread use at SBRT centers, there are limited high-quality data on the efficacy of SBRT for oligometastatic lymph node metastases. Because lymph node resection is not practiced widely for metastatic disease and can be technically challenging and morbid, SBRT is often the preferred treatment option for these patients and can offer them periods free from the toxicities of systemic therapy. In a retrospective study of 18 patients treated with SBRT for lymph node oligometastases from various primary tumors (seven CRC), a 1-year local control rate of 94% was observed and 1-year overall survival rate was 89%. No CTCAE grade 3 or greater toxicities were observed. In general, doses ranging from 36 to 51 Gy in three to five fractions have been used; careful recording of acute and late toxicities is advised to ensure adequate clinical governance.

Selective Internal Radiotherapy for Liver Metastasis

Selective internal radiation therapy (SIRT) with resin or glass microspheres labeled with the β-emitter 90Y enables targeted delivery of radiation to inoperable liver metastases from CRC. Whereas SBRT delivers high doses of external radiation in fractions, SIRT delivers a continuous dose of radiation inside the liver. The physical half-life of 90Y is 64 hours, so patients must be aware of some simple radiation protection precautions for up to 7 days after SIRT. The treatment involves a workup procedure during which hepatic angiography is performed, aberrant vessels from liver to other organs are embolized with coils, and 99mTc-labeled macro-aggregated albumin is injected as a surrogate of the treatment. The definitive treatment procedure is performed within 2 to 3 weeks of the workup procedure, during which millions of 90Y microspheres are injected directly into the hepatic arterial vasculature. Because the 90Y-loaded microspheres preferentially localize in tumor arterial vasculature, very high radiation doses are delivered to tumors while tolerable radiation doses to normal hepatic tissue are maintained.

In mCRC, SIRT is predominantly used as salvage therapy in treatment-refractory disease or in the second-line settings in combination with chemotherapy. Hendrix and colleagues randomly assigned 46 patients with mCRC refractory to standard chemotherapy to protracted intravenous infusional 5-fluorouracil or the same chemotherapy (dose reduced) plus SIRT; they observed an improvement in median time to tumor progression of 2.4 months in favor of the combination treatment. Because of crossover to SIRT treatment from the control arm, overall survival could not be studied meaningfully. On the basis of this randomized controlled trial and published cohort studies, SIRT is widely reimbursed in high-income countries for the treatment of mCRC.
mCRC refractory to chemotherapy. There exists recently published guidance on the optimal approach to managing some of the most important complications of SIRT.85

The combination of SIRT with first-line chemotherapy is not widely used in clinical practice. The feasibility of combining SIRT with first-line FOLFOX chemotherapy as a combined radiosensitization approach for mCRC had been previously demonstrated by Sharma and colleagues in 2007.86 The FOXFIRE-SIRFLOX-FOXFIRE Global combined analysis of 1,103 patients assessed the efficacy and safety of SIRT with 90Y resin microspheres when combined with first-line FOLFOX chemotherapy versus FOLFOX alone in patients with liver-only or liver-dominant mCRC (bevacizumab or other biologically targeted agent was allowed at the discretion of the investigators). This combined analysis demonstrated that despite improving objective response rate and liver-specific progression, the addition of SIRT did not affect overall survival and increased the frequency of grade 3 to 5 adverse events.87 The median improvement in local control of liver metastases exceeded 8 months,84 but the amount of chemotherapy and other antitumor therapy received by patients in the combination arm was significantly lower than that in patients randomly assigned to the control arm. Because approximately 16% of patients in these prospective clinical trials proceeded to have surgical resection of liver metastases after SIRT,89 current data suggest that liver surgery is safe after SIRT, as suggested by a recently published surgical series.85

In summary, recent advancements in systemic therapy, external and internal radiotherapy, and interventional radiology have substantially expanded our therapeutic armamentarium. A coordinated multidisciplinary strategy is required to integrate these nonsurgical adjuncts in an evidence-based manner to optimize outcomes for patients with potentially resectable metastatic disease.

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References


Approximately one in 20 Americans will develop colorectal cancer (CRC) in their lifetimes. Population CRC prevention by screening colonoscopy for average-risk individuals begins at age 50 and generally is repeated every 10 years. Precision CRC prevention connotes a tailored approach to screening for CRC, in which the differential use of preventive strategies like colonoscopy or chemoprevention are based on individual and/or group-specific risks. Although much of the practice of medicine is still conducted in a one-size-fits-all fashion, increasing costs and growing recognition of variability in cancer risk that results from measurable genetic risk factors and adverse environmental, dietary, or occupational exposures have fueled the development of guidelines in preventive oncology that help clinicians stratify patients by risk in an effort to optimize screening and prevention. The growing and increasingly complex list of personal history, family history, and genetic risk factors that are now included in many guideline statements are evidence of the centrality of precision in current CRC prevention practices and will be the focus of this discussion.

**PREVENTION**

**Why is Precision CRC Prevention Necessary?**

Precision in CRC prevention is critical in the face of increasing health care costs, limited resources, and the notion that cancer prevention can be conducted most efficiently when it is tailored to an individual’s specific level of risk. For CRC, this means low- to average-risk individuals may be spared a portion of the morbidity associated with aggressive prevention efforts (e.g., risk of frequent colonoscopy, including perforation; the risk of aspirin for CRC prevention, such as gastritis and bleeding), whereas high-risk individuals should be offered screening beyond that of the average person to reduce cancer incidence and mortality. For the sake of precision, current CRC prevention efforts consider a variety of factors. Family history is among the most common factors used to guide precision medical care in a variety of disease sites and is a core element of all CRC screening guidelines, clinicians should be familiar with these guidelines (which are not discussed in this article). Today’s multigene testing panels—which began with the cloning of the APC gene (associated with familial adenomatous polyposis) and the mismatch repair (MMR) genes of Lynch syndrome in the 1990s—can delineate risk for a small yet distinct portion of familial CRC, although the lion’s share of familial CRC is still unexplained by detectable mutations in hereditary risk genes. Group-level risk associated with race and/or ethnicity also is recognized in recommendations from some expert groups. Finally, the gastrointestinal clinician’s consideration of previous screening findings (e.g., adenoma free on a previous colonoscopy vs. a large tubulovillous adenoma vs. sessile serrated adenoma) and other health factors (e.g., history of inflammatory bowel syndrome) round out the factors currently considered when colonoscopy intervals are tailored to the individual patient.
Operationalizing the Practice of Precision CRC Prevention

Examples of some of the core relevant strata by which current precision CRC prevention approaches are recommended by different expert groups are listed in Table 1. Guidelines that incorporate the impact of environmental exposures and dietary factors on recommended screening intervals; comorbid health conditions, like obesity; or past use of medications that may modulate CRC risk, like aspirin or statin use, remain limited. At least one risk calculator to integrate family history, lifestyle factors (like smoking), and screening history to determine lifetime CRC risk in average risk individuals has been developed and is available through the National Cancer Institute website, but it does not incorporate genetic risk factors. More advanced tools to tailor recommended screening to individual-level medical, genetic, and exposure-related factors are a critical challenge to the success of precision CRC prevention.

Precision CRC According to Personal and Family History

A family history of CRC is among the strongest predictors of personal CRC risk: risk is highest among those individuals with one or more first-degree relatives with CRC. A portion of this familial risk can be explained by shared inherited genetic risk factors, such as moderate- and high-penetrance genetic mutations in hereditary risk genes, such as the MMR genes of Lynch syndrome, but most familial risk is not explained by this mechanism. Some families will demonstrate very strong familial risks that meet strict high-risk criteria, such as the Amsterdam I criteria for risk, but upon testing do not have features of a known hereditary cancer syndrome. Assignment of risk in these families remains a challenge. Occurrences of early-onset CRC have been increasing, and it is associated in some cases with a hereditary cancer risk. A recent population-based study has identified germline mutations in approximately 25% of individuals with early-onset CRC. In addition to CRC onset before age 50, a family history of advanced/high-risk adenomas in the colon has been associated with increased cancer risks in close relatives and should be considered when making CRC screening recommendations.

Personal history of colorectal polyps, including multiple and right-sided hyperplastic polyps, high-risk and multiple adenomatous lesions, and sessile serrated adenomas are all recognized as sources of increased risk of CRC and merit more frequent CRC screening. Several U.S.-based studies in recent years have documented a distinct increase in incidence of and mortality as a result of CRC among young individuals (< age 50) during the past 30 to 40 years; since 2000, incidence has increased 22% and mortality, 13%; however, a clear cause has not been established. Although the higher risk of CRC among older individuals living in developed nations appears linked to dietary and lifestyle factors related to socioeconomic status, it remains uncertain what risk factor(s) may be driving the increasing CRC rates in young adults. It also remains uncertain whether there are other increased cancer risks in this group, such as increased risks of second CRC, upper gastrointestinal cancers, or other cancers. CRC survivors are a particularly important group that has increased risks of a second CRC, and chemoprevention with low-dose aspirin is now recommended for survivors. Finally, a personal history of inflammatory bowel syndrome, including Crohn disease and ulcerative colitis, also increases the risk of CRC and supports recommendations for CRC screening tailored to the specific disease, duration since diagnosis, extent of bowel involvement, and activity.

Precision CRC Prevention According to Germline Genetic Risk

CRC risk stratification that is based on germline genetic risk factors is a rapidly evolving area of hereditary CRC prevention. As listed in Table 1 and as detailed in the updated 2017 National Comprehensive Cancer Network guidelines, germline mutations in multiple genes now have been shown to confer an increased risk of CRC, and risk ranges from a 10% lifetime risk to a nearly 80% to 100% lifetime risk of CRC. What is generally true in hereditary/genetic risk is that the highest-risk gene mutations tend to be rarer in the population, and asymptomatic carrier rates are relatively low. These truths are exemplified by those mutations in...
the APC gene associated with classic familial adenomatous polyposis; mutations in the GREM1 gene; and mutations in the higher-penetrance MMR genes, MLH1 and MSH2. Conversely, moderate- to low-penetrance gene mutations tend to be more common to extremely common and may be found frequently among individuals with no personal or family history of cancer. Examples of these mutations include mutations in the MMR genes MSH6 and PMS2, monoallelic mutations in the MUTYH gene, low-penetrance mutations in the APC I1307K gene, and—potentially—a host of other mutations in genes for which contributions to CRC risk are still being defined (e.g., ATM, CHEK2, BRCA1/2, CDH1). Among high-risk gene mutation carriers, precision recommendations may be as aggressive as total colectomy for patients with classic familial adenomatous polyposis or for biallelic MUTYH carriers, but recommendations are often softened and tailored to polyp density and the presence of rectal involvement (and the possibility of rectal sparing) in those with less-dense polyposis. High-risk patients with Lynch syndrome, though, should undergo frequent (1- to 2-year) colonoscopies because of the risk of even small adenomas developing into cancer and the risk of rapid progression.

### TABLE 1. Example Clinical Factors Used to Guide Precision CRC Prevention

<table>
<thead>
<tr>
<th>Precision Factor by Guideline</th>
<th>Relevant Stratification</th>
<th>Screening/Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Comprehensive Cancer Network Guidelines, v.2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history of CRC, no genetic risks</td>
<td>FDR with CRC, any age</td>
<td>Early, increased frequency (5–10 years)</td>
</tr>
<tr>
<td></td>
<td>FDR with advanced adenoma</td>
<td>Early, increased frequency (5–10 years)</td>
</tr>
<tr>
<td></td>
<td>SDR with CRC &lt; 50 years</td>
<td>Increased frequency (5–10 years)</td>
</tr>
<tr>
<td>Personal history of polyps or adenomas</td>
<td>Low risk (TA; SSA ≤ 2, &lt; 1 cm; negative HGD)</td>
<td>Increased frequency (5–10 years)</td>
</tr>
<tr>
<td></td>
<td>High risk (TVA/VA; SSA or TA &gt; 1 cm, positive HGD; 3–10 TA)</td>
<td>Greatly increased frequency (3–5 years)</td>
</tr>
<tr>
<td></td>
<td>Possible genetic risk (&gt; 10 adenomas)</td>
<td>Refer to genetics</td>
</tr>
<tr>
<td></td>
<td>Piecemeal endoscopy</td>
<td>Increased frequency (2–6 months)</td>
</tr>
<tr>
<td>Personal history of IBS</td>
<td>&lt; 8 years of IBS, well-controlled disease</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>≥ 8 years of IBS, poorly controlled disease</td>
<td>Increased frequency, biopsy, HD-WLE, or chromoendoscopy</td>
</tr>
<tr>
<td>Findings at screening</td>
<td>Low risk: L sided, dysplasia, or inflammation</td>
<td>Greatly increased frequency (2–3 years)</td>
</tr>
<tr>
<td></td>
<td>High risk: PSC, extensive colitis, inflammation, family history of CRC &lt; 50 years, adenomatous polyps, pseudopolyps, dysplasia, stricture</td>
<td>Increased frequency (1 year)</td>
</tr>
<tr>
<td></td>
<td>If large dysplastic (≥ 1.5 cm), then chromoendoscopy 3–6 months</td>
<td></td>
</tr>
<tr>
<td>Hereditary/genetic risk of cancer</td>
<td>Polyposis genes: APC (FAP), biallelic MUTYH (MAP), STK11 (PIS), POLE/D1 (PAPP), GREM1, BMPR1A, SMAD4, PTEN (CS), NTHL1, AXIN1, MSH3</td>
<td>Very early (gene dependent; some begin in adolescence)</td>
</tr>
<tr>
<td></td>
<td>Nonpolyposis genes: MLH1/MSH2/EPCAM (Lynch); TP53 (LFS)</td>
<td>Increased frequency (gene dependent, some yearly)</td>
</tr>
<tr>
<td>Higher-risk syndromes GENes</td>
<td>Nonpolyposis genes: MSH6/PMS2 (Lynch)</td>
<td>Early, increased frequency (but later start/less frequent than MLH1/MSH2 carriers)</td>
</tr>
<tr>
<td>Moderate- and lower-risk genes</td>
<td>Nonpolyposis genes: APC I1307K, CHEK2, monoallelic MUTYH</td>
<td>Early, increased frequency (5–10 years)</td>
</tr>
<tr>
<td>U.S. Multi-Society Task Force</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic characteristics</td>
<td>African American</td>
<td>Early (45 years)</td>
</tr>
<tr>
<td>Race</td>
<td>Age ≥ 75 or life expectancy &lt; 10 years</td>
<td>Suspend screening</td>
</tr>
<tr>
<td>High-risk family histories</td>
<td>Family colon cancer syndrome X</td>
<td>Family meets Amsterdam criteria but tumor mismatch repair testing is intact</td>
</tr>
<tr>
<td>U.S. Preventive Services Task Force</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRC prevention with low-dose aspirin</td>
<td>Adults age 50–59 with ≥ 10% 10-year CVD risk</td>
<td>Daily 81 mg ASA for ≥ 10 years</td>
</tr>
</tbody>
</table>

Abbreviations: ASA, aspirin; CRC, colorectal cancer; CS, Cowden syndrome; CVD, cardiovascular disease; FAP, familial adenomatous polyposis; FDR, first-degree relative; HGD, high-grade dysplasia; IBS, irritable bowel syndrome; LFS, Li-Fraumeni syndrome; MAP, MUTYH-associated polyposis; PAPP, polymerase proofreading-associated polyposis; PJS, Peutz-Jeghers syndrome; PSC, primary sclerosing cholangitis; SDR, second-degree relative; SSA, sessile serrated adenoma; TA, tubular adenoma; TVA, tubulovillous adenoma.
of lesions to cancer when longer screening intervals are adopted.5,38,39

Although the list of hereditary CRC risk genes continues to grow, Chubb et al40 and Dobbins et al41 have proposed that the majority of high-penetrance CRC risk genes have already been discovered. Nonetheless, a large fraction of familial CRC remains undefined by germline genetic factors and is likely related to mixed environmental and/or shared exposures, shared dietary patterns, factors associated with a shared microbiome, epigenetic risk factors, and other reasons.42-45 One area that has been relatively underdeveloped in precision CRC prevention compared with breast cancer research is the concept of residual risk.46 In breast cancer, familial mutations may explain only a portion of the breast cancer risk within a high-risk family. Testing mutation negative (also known as true negative) in this setting may mitigate but not totally eliminate elevated cancer risks seen in some families.47-49

Precision CRC Screening According to Race/Ethnicity
Data from the national population-based Surveillance and Epidemiology and End Results database highlight the higher risk for, and earlier age of onset in, CRC among African Americans compared with other Americans.50-53 In part because of the lower uptake of colonoscopy screening in the African American population and other factors, increased risk by race/ethnicity has been one factor underlying disparities in CRC survival between African American and white patients.54,55 Although disparities have often highlighted differences between black and white patients, disparities in CRC screening and outcomes are found in other minority populations, too.45 In 2005, the American Gastroenterological Association Committee of Minority Affairs and Cultural Diversity lowered the age of colorectal screening initiation to age 45 for individuals of African ancestry.57 The current U.S. Multi-Society Task Force1 guidelines for CRC continue to recommend screening to begin at age 45 for African Americans.

The Future of Precision CRC Prevention
Precision CRC prevention will continue to evolve as a more granular understanding of known CRC risk factors is achieved and as new factors that differentially affect risk are identified. For example, evidence suggests that the risk of CRC associated with ulcerative colitis may be decreasing because of a variety of factors, including more widespread use of anti-inflammatory agents and immunomodulators.58-60 In the area of hereditary cancer risks, efforts already are underway by several groups to improve gene-specific and potentially even mutation-specific estimates of cancer risk and penetrance in the MMR genes.51,62 Efforts also are ongoing to continue to understand the scope of disease risk by gene, and a growing body of literature cites new risks of breast cancer and potentially other cancers in Lynch syndrome mutation carriers.63-65 The incorporation of single-nucleotide polymorphisms and other genomic markers into residual risk estimates in patients with strong family history but no detectable mutation, or in patients with early-onset cancer without a detectable mutation, will be increasingly valuable to tailoring screening and prevention.46,48 Risk calculators like the recently updated PREMM5 model also will be critical to broadly screen the population for patients who may benefit from germline testing in an effort to offer improved precision to CRC screening plans.66 Even more powerful, however, will be risk tools that consider multiple factors of risk at the individual level. Such integrated risk models will incorporate population and individual genetic risks in the context of personal history of environmental, dietary, and other risk factors to offer patients improved estimates of CRC as well as information about how and to what degree risks may be reduced through screening, healthy lifestyle, risk factor avoidance, and chemoprevention.

ADJUVANT CHEMOTHERAPY IN COLON CANCER

The Goal and Rationale of Adjuvant Therapy
Evidence demonstrates that approximately 25% to 40% patients will develop a tumor recurrence as a locoregional recurrence, distant metastasis, or metachronous colorectal lesions despite receiving a potentially curative operation.67 The goals of adjuvant therapy are to evaporate potential present microscopic metastatic cancer cells after curative-intent surgery and to decrease the recurrence and metastases of the disease, which thus increases cure rate and overall survival.68 The decision about specific adjuvant therapy is based on the assessment of statistic evidence of disease relapse. Because the treatment is essentially for a risk, rather than for provable disease, it is accepted that a proportion of patients who receive adjuvant therapy were already cured by their primary surgery. Therefore, minimization of the short-term and long-term toxicities is an important factor.

Recurrence Risk Assessment in Colon Cancer
The assessment of recurrence risk in colon cancer is still based mainly on the pathohistology characteristics of a patient’s disease at the surgery. The anatomic TNM classification remains the only validated prognostic tool in the adjuvant setting, and clinical practice is based on T and N staging. The American Joint Committee of Cancer updates the staging systems every 6 years according to new evidence from clinic research and epidemiologic data to keep information as precise and accurate as possible. The eighth edition of the staging guideline was published in January 2018.69 The Union for International Cancer Control also updates its staging guidelines regularly, for the same purpose.70 With the recent research advances in molecular biology and translation medicine, myriad candidate molecular biomarkers have been reported for prognosis and for prediction of therapy. However, the application of these markers in clinical practice to guide adjuvant therapy remains limited, because rigorous assessment in large patient data sets by multivariable analysis, and subsequent implementation and validation, is needed.71-74 In colon cancer, the clinical decision to use adjuvant chemotherapy remains based almost entirely on
the T and N staging system. Data from large bodies of evidence from randomized clinical studies have identified clear survival benefits of adjuvant chemotherapy in patients with stage III colon cancer.67,68

Argument, Debate, and Consensus of Stage II Colon Cancer
For patients with cancer that invades the muscularis propria but has no lymph node involvement (stage IIA), general recommendations suggest that adjuvant chemotherapy may not contribute enough benefit in overall survival. Enough evidence has demonstrated that adjuvant chemotherapy with fluorouracil (FU) alone may cause detriment in patients with stage II colon cancer and MMR deficiency.75,77 However, it is well known that the prognosis of patients with stage II tumors that penetrates to the surface of the visceral peritoneum (T4a) and that directly invade or adhere to other organs or structures (T4b) may be worse than that of patients with T3N1 disease. Therefore, discussion about and consideration of adjuvant chemotherapy is warranted in those patients with so-called high-risk stage II disease, defined by the following factors: T4 lesions, clinical presentation with bowel obstruction or perforation, fewer than 12 lymph nodes recovered in the specimen, and poor differentiation histology.78 A high level of baseline carcinoembryonic antigen (i.e., > 5 ng/L), large vessel invasion, and perineural and extramural vascular invasion also are considered risks associated with recurrence.79 Other factors, such as age, comorbidities, and personal preferences, may affect the decision about adjuvant therapy.

Development and Choices of Adjuvant Treatment Regimens
Adjuvant therapy in the colon was first introduced into clinical practice in the early 1960s, shortly after the anticancer efficacy of FU was demonstrated in advanced colon cancer.80 Since the mid-2000s, 6 months of either FOLFOX or XELOX for XELOX and FU/FA were 77.6% and 74.2%, respectively (HR 0.80; 95% CI, 0.68–0.93; p = .003). The 6-year overall survival rates were 78.5% and 76.0% in the FOLFOX4 and infusional groups, respectively (HR 0.84; 95% CI, 0.71–1.00; p = .046). The 6-year overall survival rates in only stage III disease were 72.9% and 68.7%, respectively (HR 0.80; 95% CI, 0.71–1.00; p = .046). The 6-year overall survival rates in only stage III disease were 72.9% and 68.7%, respectively (HR 0.80; 95% CI, 0.65–0.97; p = .023). The benefits of oxaliplatin with the combination of capecitabine in the adjuvant setting were confirmed in a study that compared bolus FU/leucovorin (e.g., oxaliplatin plus capecitabine [XELOX, CAPOX]).89,91 In the X-ACT trial, patients with stage III colon cancer were randomly assigned to XELOX (oxaliplatin plus capecitabine) or to an FU/leucovorin adjuvant regimen. The 3-year DFS rate was 70.9% with XELOX and was 66.5% with FU/leucovorin. The 5-year overall survival rates for XELOX and FU/FA were 77.6% and 74.2%, respectively. Since the mid-2000s, 6 months of either FOLFOX or XELOX has been a standard adjuvant treatment choice for stage III colon cancer.

IDEA Consortium
The major challenge of FOLFOX or XELOX in clinic practice is the oxaliplatin-associated dose-related neuropathy, which affects the quality of life in almost all patients during therapy and which may greatly affect some patients for a long
time after treatment is finished. Because the success of attempts to minimize the dose-related neuropathy without compromising efficacy by calcium or magnesium infusion during oxaliplatin admission was not confirmed in a phase III study, the focus turned to alteration of the duration of treatment by reducing the cumulative doses of oxaliplatin. Interestingly, a multicenter randomized study with 801 patients demonstrated that 12 weeks (3 months) of adjuvant infusion FU was associated with significantly better quality of life during treatment and faster time to recovery compared with 6 months of bolus FU/leucovorin.

The IDEA (International Duration Evaluation of Adjuvant chemotherapy) prospective, preplanned accumulated data from six large randomized trials worldwide (i.e., SCOT, TOSCA, Alliance/SWOG 80702, IDEA France [GERCOR/PRODIGE], ACHIEVE, and HORIG) evaluated the noninferiority of 3 months compared with the standard 6 months of adjuvant FOLFOX/XELOX for patients with stage III colon cancer. The primary endpoint was DFS, defined as time from enrollment to relapse, second colorectal cancer, or death as a result of any cause. Noninferiority was declared if the two-sided 95% CI for the disease-free hazard ratio (3 months vs. 6 months) estimated by a stratified Cox model was less than 1.12. Preplanned noninferiority was examined within regimen and stage subgroups. The data were presented at the 2017 ASCO Annual Meeting. More than 12,000 patients from 12 countries were included in the analysis; the stage distribution was as follows: 13%, T1 to 2; 66%, T3; 21%, T4; and 28%, N2. Overall, 60% of patients received FOLFOX, and 40% received XELOX. The result showed that rates of grade 3 or greater neurotoxicity were higher in the 6-month arm versus the 3-month arm (16% vs. 3% with FOLFOX, 9% vs. 3% with XELOX; both p < .0001). Grade 2 neurotoxicity rates also were greater in the 6-month arm versus the 3-month arm (32% vs. 14% with FOLFOX, 36% vs. 12% with XELOX; both p < .0001). During a median follow-up time of 39 months, 3,263 DFS events were observed. Overall, the 3-year DFS rate was 74.6% in the 3-month arm and was 75.5% in the 6-month arm; the estimated DFS HR was 1.07 (95% CI, 1.00–1.15). The authors concluded that the DFS noninferiority of 3 months with oxaliplatin-based adjuvant therapy was not established overall in stage III colon cancer. Interestingly, the subgroup analyses showed that the 3-month versus the 6-month DFS HR was 1.16 (95% CI, 1.06–1.26) for FOLFOX and was 0.95 (95% CI, 0.85–1.06) for XELOX. The 3-months versus 6-month DFS HR was 1.01 (95% CI, 0.90–1.12) in T1-3N1 disease and was 1.12 (95% CI, 1.03–1.23) in T4 or N2 diseases. The data for these subgroup analyses suggest that the choice of regimen (FOLFOX vs. XELOX) and risk group (T1-3N1 vs. T4 or N2) should be considered in discussions about the noninferiority of 3 months of oxaliplatin-based adjuvant therapy: noninferiority was indicated with XELOX and in the T1-3N1 subgroup stage.

Clinical Application in Practice

How to apply the data of IDEA collaboration into routine medical oncology clinic practice is an important issue in the clinic. First, we must understand that the primary endpoint of IDEA was 3-year DFS. Although 3-year DFS is a validated surrogate endpoint of overall survival, long-term overall survival data are needed to make a final conclusion. First, IDEA contained accumulated data from different studies, which resulted in unbalanced studies and regimens (e.g., FOLFOX vs. XELOX). IDEA was not designed to compare different regimens. Second, multiple variations, not only in T and N stages, exist among patients with stage III colon cancer. Third, the duration of adjuvant therapy aimed mainly to decrease the oxaliplatin-associated dose-dependent and cumulative neurotoxicity. Furthermore, the development and advances in molecular/biologic predictive and prognostic markers will influence our judgement of and decision about adjuvant therapy. Therefore, detailed discussion between physicians and patients is needed to consider all potentials and concerns. Thus, the consensus of oncologists may not be able to follow clear standards when they are faced with similar clinical scenarios. Instead of rigidly or dogmatically making a decision of 3 versus 6 months of adjuvant therapy up front, the therapy could be initiated for 6 months as the target with a plan of alternating the treatment duration on the basis of a neurotoxicity assessment (toxicity grade and tolerance of the patient). Three months of therapy should be the minimal requirement, even in patients with relatively lower risk (e.g., T1-3N1 disease). For those patients with high risk (T4 or N2 disease), all supportive efforts should be given to complete 6 months of therapy. XELOX could be considered a preferred regimen of choice, especially in those patients for whom the decision of 3 months of therapy is already made up front.

SURVEILLANCE

Rationale and Guidelines

Current evidence suggests improved rates of curative secondary treatment with surveillance after potential curative resection of colon cancer, which has been considered standard in oncologic practice. Approximately 25% to 40% of patients will develop tumor recurrence as locoregional recurrence, distant metastasis, or metachronous colorectal lesions despite a potentially curative operation. Data from meta-analyses and randomized controlled studies showed that surveillance by periodic images and monitoring of carcinoembryonic antigen levels likely are associated with early detection of asymptomatic recurrences, which therefore increases the potential for curative therapy and survival benefit. Long-term survival can occur after complete resection of local regional recurrences and of metastatic liver and lung recurrences. Detection of asymptomatic metachronous colorectal lesions, including cancer and polyps via scheduled colonoscopy, may also lead to a cure. However, the optimal strategy to accurately detect recurrences at the earliest stage remains controversial. Currently, the general recommendations for follow-up surveillance include a combination of history and physical examination, laboratory and imaging evaluation, plus endoscopy (with somewhat slightly varying schedules) according to the stage of disease.
surveillance by PET scan in lieu of traditional CT scanning, for high-risk patients. There is no sufficient evidence about annual image surveillance appears common for average-risk patients, with the knowledge that the most common sites of systemic recurrence for colorectal cancer are the liver and the lung. However, there are no trial data about the optimal frequency of surveillance imaging. Improved survival of recurrence was observed with CT scans administered at a frequency of every 3 to 6 months, but this schedule has not been compared with a less frequent protocol. Therefore, there is no universal agreement about the frequency of imaging; annual image surveillance appears common for average-risk patients, and more frequent imaging may be considered for higher-risk patients. There is no sufficient evidence about surveillance by PET scan in lieu of traditional CT scanning, although it has been used to help select patients for hepatic resection and to evaluate patients with an elevated carcinoembryonic antigen who had normal conventional imaging and colonoscopy results.

### Stages II and III

All guidelines strongly recommend comprehensive surveillance for patients with stage II and stage III colorectal cancer after curative resection with or without adjuvant chemotherapy. The generally recommended frequency of the comprehensive surveillance is every 3 to 6 months for the first 2 years and then twice a year for a total of 5 years. Regularly scheduled office visits and carcinoembryonic antigen testing are included. A pooled analysis from the ACCENT database of 18 clinical trials that included patients with stages II and III colon cancer supports the decreasing the frequency of surveillance testing over time. In this study with 20,898 patients, 5,722 (33%) experienced recurrence after FU-based adjuvant therapy. Among patients with disease recurrence, 62% were identified within the first 2 years; 80%, within 3 years; and 92%, within 4 years. After 5 years, the recurrence rate was less than 1.5% per year. After 10 years, the recurrence rate was rare (less than 0.5% per year). The FACS trial found that carcinoembryonic antigen testing either alone or in combination with CT was associated with an increase in the number of patients with disease recurrence who could be treated with curative intent. Routine radiographic surveillance, including cross-sectional chest and abdomen and pelvis images (CT or MRI), are recommended, with the knowledge that the most common sites of systemic recurrence for colorectal cancer are the liver and the lung. However, there are no trial data about the optimal frequency of surveillance imaging. Improved survival of recurrence was observed with CT scans administered at a frequency of every 3 to 6 months, but this schedule has not been compared with a less frequent protocol. Therefore, there is no universal agreement about the frequency of images; annual image surveillance appears common for average-risk patients, and more frequent imaging may be considered for higher-risk patients. There is no sufficient evidence about surveillance by PET scan in lieu of traditional CT scanning, although it has been used to help select patients for hepatic resection and to evaluate patients with an elevated carcinoembryonic antigen who had normal conventional imaging and colonoscopy results.

### Stage IV After Curative-Intent Surgery

Patients with metastatic colorectal cancer who successfully undergo potentially curative–intent therapy typically undergo surveillance routinely, but the potential benefit of the surveillance remains somewhat controversial. Long-term survival benefit is well documented in properly selected patients who receive curative therapy, especially those patients who have isolated disease, even after secondary intervention for recurrent disease. Guidelines from both the National Comprehensive Cancer Network and the American Society of Colon and Rectal Surgeons agree to continue surveillance in those with no evidence of disease. The timing and duration of surveillance are debatable, and both are determined basically by the individual patient risk profile and performance status. A recent retrospective cohort study analyzed the recurrent models in 1,070 patients with metastatic colorectal cancer who had potentially curative–intent resections (R0 resections for both primary and metastatic diseases). The data showed the overall rate of recurrence was 73% (784 of 1,070 patients); 62% of recurrences developed within 1 year (as early recurrence), 24% developed in 1 to 2 years (as middle recurrence), and 14% developed in 2 or more years (as late recurrence). The study indicated that risk factors for early recurrence included site (rectum), depth of tumor invasion (T4), increasing N stage, venous invasion, and liver metastasis. Risk factors for later recurrence were tumor size of 50 mm or smaller and peritoneal dissemination. These data may help guide surveillance protocol after curative resection of stage IV colorectal cancer.

### Other Issues

There are no clear surveillance recommendations for stage I colorectal cancer except for scheduled colonoscopy, because there are little definitive data about surveillance effectiveness. It is notable that recurrences do happen in patients with stage I colorectal cancer after resection. All guidelines recommend performance of surveillance colonoscopy at 1 year after curative resection for patients with surgically treated stage I to IV colorectal cancer. Subsequent colonoscopy should be performed every 3 to 5 years depending on the findings at the first postoperative examination. In cases of incomplete colon evaluation before surgery, the initial colonoscopy should be performed within 3 to 6 months or upon the completion of adjuvant therapy. This recommendation is based on reports of a high incidence of apparently metachronous second cancers in the first 2 years after resection. If the examination at 1 year is normal, then the interval of surveillance thereafter should be 3 years. If that colonoscopy is normal, then the next interval should be 5 years. Shorter intervals may be indicated according to associated adenoma findings or if the patient’s age, family history, or tumor testing indicate definite or probable hereditary nonpolyposis colorectal cancer. Liquid biopsy that is based on circulating tumor cells and ctDNA analysis has shed a new light on the molecular diagnosis and monitoring of cancer, including colorectal...
cancer. Studies suggest that the screening of circulating tumor cells and ctDNA may be highly sensitive, which may significantly improve tumor diagnosis and facilitate early-stage detection. Therefore, use of circulating tumor cells ctDNA as a liquid biopsy may herald a revolution for tumor management in the future. However, the clinical applicability is still at the research level. The results depend on the volume of plasma and the technology used for analysis. Prospective studies are needed, and promising results should be validated in large follow-up studies to ensure clinical applicability. Also, a deeper understanding of cancer biology may lead to improved insight into how and when liquid biopsies may be of best clinical use.

It is important to point out that the success of surveillance for early detection of curable recurrence depends on patient and provider adherence to the surveillance schedule and avoidance of unnecessary examinations. An equally important factor is that, after curative resection of colorectal cancer, patients are still at risk for other common malignancies (e.g., lung, breast) for which standard screening recommendations should be observed and measures to maintain general health should be recommended.

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Molecular Subtypes and the Evolution of Treatment Decisions in Metastatic Colorectal Cancer

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OVERVIEW

Colorectal cancer (CRC) has clinically relevant molecular heterogeneity at multiple levels: genomics, epigenomics, transcriptomics, and microenvironment features. Genomic events acquired during carcinogenesis remain drivers of cancer progression in the metastatic setting. For example, KRAS and NRAS mutations define a population refractory to epidermal growth factor receptor monoclonal antibodies, BRAFV600E mutations associate with poor outcomes under standard therapies and response to targeted inhibitors in combinations, and HER2 amplifications confer unique sensitivity to double HER2 blockade. Multiple rare gene alterations driving resistance to epidermal growth factor receptor monoclonal antibodies have been described, with substantial overlap in primary and acquired mechanisms, in line with a clonal selection process.

In this context, sequential analysis of circulating tumor DNA has the potential to guide drug development in a treatment-refractory setting. Rare kinase fusion events and complex alterations in genes involved in DNA damage repair have been described, with emerging evidence for targetability. On the other hand, transcriptomic subtypes and pathway activation signatures have also shown prognostic and potential predictive value in metastatic CRC. These markers reflect stromal and immune microenvironment interactions with cancer cells. For example, the microsatellite instable or POLE ultramutant CRC population is particularly sensitive to immune checkpoint inhibitors, whereas tumors with a mesenchymal phenotype are characterized by activation of immunosuppressive molecules that mandate stratified development of novel immunotherapy combinations. Here, we review the expanding landscape of targetable oncogenic alterations and signatures in metastatic CRC and discuss the clinical implementation of novel molecular diagnostic tests.

With the recent characterization of the transcriptomic subtypes of the disease (consensus molecular subtypes [CMS]), convergent pathway dependencies were identified: CMS1 (MSI immune) is hypermutated and MSI, with strong immune cell infiltration and cytotoxic signaling activation; CMS2 (canonical) is epithelial, chromosomally instable, immune desert, and shows marked WNT and EGFR signaling dependence; CMS3 (metabolic) is epithelial and has mixed chromosomal and microsatellite instability, evident metabolic dysregulation, and mutations in the MAPK pathway; and CMS4 (mesenchymal) is chromosomally instable, with prominent TGFβ activation linked to microenvironment infiltration with immunosuppressive and stromal cells. The CMS groups reflect distinct biology of primary CRC tumors and have a clear prognostic impact in early-stage and advanced disease, with CMS4 mesenchymal tumors having twofold increased chances of relapse after curative therapy and CMS1 MSI immune tumors associated with dismal prognosis in the metastatic setting.
In parallel with our increased understanding of molecular drivers and tumor-microenvironment interactions in CRC, major advances in drug development of targeted agents and immunotherapies have shown the value of tumor profiling in the clinic. Molecular heterogeneity plays an important role in treatment selection in metastatic CRC (mCRC), with KRAS/NRAS (RAS) mutated tumors intrinsically resistant to EGFR monoclonal antibodies (mAbs) and MSI tumors uniquely sensitive to immune checkpoint inhibitors. On top of these validated biomarker-drug matches, there is mounting clinical evidence that additional biomarkers are relevant for treatment stratification, such as BRAFV600E mutations and HER2 amplifications. Furthermore, longitudinal studies with liquid biopsies in the anti-EGFR resistance setting revealed substantial temporal genomic heterogeneity in mCRC as a result of clonal selection process achieved under treatment pressure.1 The possibility to use next-generation sequencing (NGS) assays that test for multiple gene alterations over time has great potential to guide drug development in molecularly defined subtypes with targetable oncogenic drivers. In this review, we detail how the precision medicine paradigm of biomarker-drug matching has evolved in the past decade and discuss future prospects for transcriptomic and microenvironment profiling to expand personalized treatment options in mCRC.

ONCOGENIC DRIVERS
RAS Mutations in Tissue and Plasma
Oncogenic mutations in RAS are found in more than 50% of CRC tumors. Despite many efforts, RAS remains an elusive therapeutic target, and its relevance in the clinics is still restrained to its role as a negative predictor biomarker of response to EGFR-targeted mAbs. However, accurate assessment of RAS status has not only clinical but also major economic relevance, so it is important to briefly describe current status and challenges on molecular diagnostic tests used in clinical practice.

First, analytical sensitivity is critical when dealing with a negative predictive biomarker: all patients with tumors labeled as RAS mutant are not eligible for anti-EGFR treatment, and those with RAS wild-type tumors have a meaningful chance of deriving clinical benefit. In a retrospective analysis of the CRYSTAL trial, patients with mCRC with tumor RAS mutant allele frequencies less than 5% were still likely to have improved survival outcomes with the addition of cetuximab to FOLFIRI in the first-line setting.3 Subsequent retrospective nonrandomized data suggested the optimal cutoff point to be at 1% for EGFR mAb treatment benefit in a chemotherapy-refractory scenario.6,7 The ULTRA prospective study in second- or third-line settings provided evidence that progression-free survival (PFS) prediction was higher when a threshold of 5% was selected, reinforcing that increasing analytical sensitivity may worsen patient selection.8 One of the potential reasons for such variability in cutoffs across studies is tumor purity heterogeneity rather than in RAS-mutant clonal heterogeneity.9 Altogether, these data suggest that patients with very low RAS mutant allele frequencies in their tumors (< 5%) may still behave as wild-type because they derive comparable benefit from anti-EGFR therapies as those without detectable RAS mutations.

Next, the analysis of circulating tumor DNA (ctDNA) is an emerging alternative to detect driver gene mutations, with approximately 90% concordance rate of RAS-mutant status in paired plasma and tissue samples.10,11 False-negative cases in plasma have been linked to low tumor burden and peritoneal metastases.11 In the clinics, prediction of treatment benefit in patients receiving anti-EGFR plus irinotecan in second- or third-line settings was equivalent if tested with tumor or ctDNA. With regard to mutation detection threshold in ctDNA, half of the patients showed mutant allele frequencies of 1% or less, reflecting analytical sensitivity differences between tissue and plasma.10

Finally, ctDNA is able to detect emerging genomic alterations in RAS and other driver genes in a large proportion of patients progressing on cetuximab or panitumumab whose tumors were initially diagnosed as wild-type.12 In most cases, multiple events coexist in the same sample, such as different KRAS, NRAS, and BRAF oncogenic variants and MET or HER2 amplifications, with newly detected alterations deriving from minor preexisting subclones in the primary tumor lesion. Repeated ctDNA analyses have shown that the percentage of KRAS-mutant alleles increases under anti-EGFR treatment exposure and rapidly declines after drug withdrawal. On subsequent follow-up, KRAS-mutant clones inversely correlate with the time since last dose of EGFR mAb and dynamically evolve on anti-EGFR rechallenge.12 In approximately one-third of the cases, EGFR extracellular domain mutations that disrupt binding of EGFR mAb binding
emerge in plasma, most frequently after long exposure to therapy and after the rise of RAS-mutant clones in ctDNA. Most important, ctDNA analysis may guide patient selection for sequential use of novel EGFR inhibitors in a treatment-refractory setting after initial response and subsequent progression to cetuximab or panitumumab. In a randomized phase II trial with Sym004, a mixture of two EGFR mAbs, patients with plasma ctDNA negative for RAS, $\text{BRAF}^{\text{V600E}}$, and $\text{EGFR}$-activating mutations at the time of treatment initiation experienced an increase in median overall survival of 5.5 months compared with standard-of-care therapies. These promising results in a molecularly selected population support the design of pivotal ctDNA-guided clinical trials in EGFR inhibitor refractory mCRC.

**BRAF Mutations**

Close to 8% of patients with mCRC harbor $\text{BRAF}^{\text{V600E}}$-mutant tumors, which are associated with resistance to anti-EGFR regimens and significantly worse survival outcomes. Matched targeted therapies for this population have evolved markedly in recent years, with better understanding of the pharmacodynamics of target inhibition (Fig. 1). CRC cells rely on $\text{EGFR}$ activation as a feedback mechanism on BRAF inhibitor exposure, with PI3K-mediated sustained MAPK signaling and activation. In early trials, combinations of BRAF plus EGFR and/or MEK inhibitors achieved response rates of 15% to 25%. A randomized phase II trial recently demonstrated a 2.4-month improvement in median PFS with the addition of vemurafenib to the control regimen of irinotecan plus cetuximab. A confirmatory study investigating doublet and triplet targeted combinations in $\text{BRAF}^{\text{V600E}}$-mutant mCRC is currently under way. Preliminary results of the BEACON trial show that the triple combination of encorafenib, binimetinib, and cetuximab has acceptable toxicity and a promising response rate of 48%.

With NGS in the clinics, $\text{BRAF}^{\text{non-V600E}}$ mutations have been identified in up to 2% of mCRC tumors, sometimes with coexisting RAS mutations. Notably, most of them have impaired kinase activity or are kinase dead, such as $\text{BRAF}^{\text{D594G}}$. In mCRC, $\text{BRAF}^{\text{non-V600E}}$ mutations do not negatively affect patient prognosis, and preclinical studies suggest that sensitivity to EGFR inhibitors is not decreased. In the clinic, when RAS-mutant alleles do not co-occur, patients may still be offered anti-EGFR-targeted agents.

**FIGURE 1. Molecular Classification of CRC and Therapeutic Implications**

(A) Genomic markers in mCRC with existing or potential matched therapies. (B) Transcriptomic markers and pathway signatures in mCRC with potential matched therapies. Abbreviations: CRC, colorectal cancer; mut, mutation; ampl, amplification; inh, inhibitors; mCRC, metastatic CRC.

*U.S. Food and Drug Administration approved.
HER2 and MET Amplifications

HER2-targeted treatment has proven very successful in HER2-amplified breast and gastric cancer. In patients with mCRC, HER2 amplification is a clinically relevant genomic alteration with prevalence of only 2% in unselected patients but a clear enrichment in left-sided RAS and BRAF wild-type primary tumors to 5%.20 HER2 status can be screened for with standard diagnostic tests and a validated cutoff of positivity using immunohistochemistry or hybridization assays is available.21 It has been linked to primary resistance to anti-EGFR agents in the refractory setting but is also a positive predictive marker for response to HER2-targeted agents in mCRC.20 In the HERACLES-A phase II trial, patients with KRAS wild-type HER2-positive tumors refractory to standard treatments were treated with the combination of trastuzumab plus lapatinib, and an overall response rate of 30% was achieved.20 Double HER2 targeting with pertuzumab and trastuzumab was explored in the phase II basket study MyPathway, with overall response rates of 38% in HER2-amplified mCRC.22 In patients with acquired resistance to anti-HER2 agents, the antibody-drug conjugate trastuzumab-DM1 has shown single-agent activity.23 These emerging data are being validated in multiple ongoing trials with different drug combinations, but no phase III trial has been initiated so far.

With regard to MET amplification in mCRC, it has been identified in numerous preclinical and clinical studies as a resistance mechanism to targeted agents, both anti-EGFR agents in RAS wild-type tumors and BRAF inhibitor combinations in BRAFV600E-mutant disease.24,25 Fewer than 2% of primary CRC tumors harbor MET amplifications, but prevalence using ctDNA NGS tests in patients refractory to anti-EGFR treatment may be as high as 20%.26 Preliminary reports suggest that potential MET inhibition in this setting can overcome resistance.27 The results of early clinical trials with novel MET-targeted agents and combinations are eagerly awaited.

Kinase Fusions

Transcriptional outlier analysis identified RAS and BRAF wild-type CRC cells resistant to EGFR blockade that are functionally and pharmacologically “addicted” to other kinase genes, including ALK, ROS1, NTRK1, NTRK2, NTRK3, and RET.28 Indeed, rare CRC patient samples with exceptionally high ALK and NTRK1 expression levels were found to harbor genomic rearrangements involving these genes, which render tumors sensitive to kinase inhibitors in preclinical models. Case reports of exceptional responses to the ALK and TRK inhibitor entrectinib in fusion positive mCRC have been reported in the literature.29,30 Despite the rarity, kinase fusions are enriched in elderly patients with right-sided MSI, RAS, and BRAF wild-type tumors, which may guide molecular testing for inclusion in tissue-agnostic clinical trials with targeted agents.31

ONCOGENIC SIGNATURES

MSI and “MSI-Like” Signature

The prevalence of MSI in the mCRC population is 5%, with most patients harboring sporadic MLH1 loss via promoter methylation/biallelic somatic genomic alterations rather than germline mutations in Lynch syndrome genes.2 MSI diagnostic tests are readily available and highly concordant: the results of immunohistochemistry panels of MMR proteins and polymerase chain reaction–based assay for detection of microsatellite loci. More recently, targeted NGS panels have also enabled highly accurate detection of a defective MMR signature on the basis of the fraction of unstable microsatellite repeats compared with control populations or through mutation burden quantification.32,33 These tumors are hypermutated because of the accumulation of base-to-base mismatches, insertion, deletions, and most frequently frameshift mutations that may generate neoantigens. Some of these neoantigens will be processed, presented by major histocompatibility complex (MHC) molecules, and recognized as foreign by T cells, which explains the high infiltration of MSI tumors with CD8-positive cytotoxic T lymphocytes and activated T helper 1 (Th1) cells characterized by interferon gamma production.34 To counterbalance this microenvironment, MSI cancer cells upregulate the expression of multiple immune checkpoints such as PD-1, PD-L1, CTLA-4, and others, thus rendering tumors particularly susceptible to immune checkpoint inhibitors.35

Pembrolizumab was tested as a single agent in a basket trial of patients with treatment-refractory progressive metastatic MSI tumors. The immune-related objective response rate in patients with mCRC was 52%, with 2-year PFS of 59% and a grade 3 to 4 adverse event rate of 20%.35 Nivolumab also showed antitumoral activity as single agent or combined with ipilimumab in patients with MSI mCRC who received a minimum of one previous standard chemotherapy regimen. Overall response rate with nivolumab alone was 31% and with the combination regimen was 55%, with a 1-year PFS rate of 71%,36,37 Grade 3 to 4 treatment-related adverse events occurred in 32% of the patients who received nivolumab plus ipilimumab.37 Predictive biomarkers for immunotherapy response in the MSI population are missing, with responses rates not influenced by PD-L1 expression, BRAF mutation status, or genetic basis for MMR deficiency.35,36 Although the clinical development of checkpoint inhibitors has not yet reached the stage of phase III trials, the remarkable antitumor activity reported have granted pembrolizumab and nivolumab U.S. Food and Drug Administration approval and National Comprehensive Cancer Network guidelines recommendation in the chemotherapy-refractory setting. Phase III randomized trials in the first-line setting are ongoing.

Of note, hypermutation rates are not exclusively seen in MSI tumors. Microsatellite-stable POLE-mutant samples, for example, have the highest mutation rates in CRC and harbor high neoantigen loads and tumor-infiltrating lymphocytes in the microenvironment. This ultramutant molecular subgroup accounts for fewer than 1% of patients with early-stage CRC and is associated with favorable prognosis.38 A case report of response to pembrolizumab in patient with chemotherapy-refractory microsatellite-stable POLE-mutant mCRC was recently published.39 Moreover, another subset
of mCRC tumors show microsatellite stability in standard diagnostic tests but test positive for an “MSI-like” gene expression signature.40 It is expected that up to 10% of mCRC cases display an “MSI-like” phenotype, and their high mutation load and dependence on angiogenic factors in silico models have supported the design of a prospective clinical trial with atezolizumab plus bevacizumab under the MoTriColor H2020 project.

Other DNA Repair Deficiency Alterations
In addition to alterations of MMR genes, CRC tumors may harbor genomic and epigenomic events in other genes implicated in DNA damage repair. In preclinical models, CRC cells with ATM loss have defective homologous recombination and show increased sensitivity to PARP inhibitors.42 Another example is MGMT promoter methylation and response to the cytotoxic alkylating drugs temozolomide and dacarbazine. In mCRC tumors selected for MGMT deficiency through combined assessment of protein expression by immunohistochemistry and percentage of promoter methylation by methyl-BEAMing, response rates in phase II trials with alkylating agents in chemotherapy-refractory setting exceeded 70%, with median PFS of 5 months.43 More recent preclinical studies have investigated the impact of temozolomide on neoantigen load and induction of immune cell infiltration of the tumor microenvironment. In mouse models, inactivation of MMR with the alkylating drug increased mutational load and promoted continuous renewal of neoantigens, which triggered immune surveillance.44 This study opens the door to rational chemotherapy plus immunotherapy combinations in molecularly defined mCRC populations.

Mesenchymal or “TGFβ-Active” Signature
The identification of actionable targets in tumors displaying a mesenchymal transcriptional phenotype is of major interest, considering the high prevalence of this signature in mCRC (25%–30%) and reduced sensitivity to standard chemotherapies.44,45 RAS wild-type CMS4 mesenchymal tumors appear to be intrinsically resistant to anti-EGFR agents in preclinical models.45,46 Moreover, retrospective analyses of clinical trials have shown similar results, also when cetuximab is given in combination with oxaliplatin-based chemotherapies.47 In mice, the use of TGFβ-signaling inhibitors to block the cross-talk between cancer cells and the microenvironment was shown to halt disease progression of stromal-enriched CRC tumors.48 Another strategy to reverse chemotherapy resistance of CMS4 mesenchymal tumors is combination therapy with chaperone (HSP90) inhibitors, an effect not seen in chemotherapy-sensitive CMS2 CRC cells and patient-derived xenograft models.45 Interestingly, both TGFβ and HSP90 inhibitors may also enhance cancer immunotherapy efficacy by upregulating T-cell cytotoxicity and interferon gamma signaling in tumors with immunosuppressive microenvironment.49,50

Despite the potential clinical utility of CRC mesenchymal signatures for outcome prediction or immune-targeted therapy development, their clinical implementation is challenging because of a lack of easy-to-use and cost-effective assays suitable for paraffin tissues. Different groups are working on classifiers based on protein markers by immunohistochemistry or gene expression signals using nCounter NanoString technology, for example, with overall accuracy close to 90% compared with the gold-standard CMS4 signature.49,51 Technical validation studies are under way, in parallel with molecularly stratified clinical trials. One example is the MoTriColor project, in which patients with mCRC with tumors testing positive for a “TGFβ-active” gene expression signature in archived paraffin tissue are eligible to the combination of galunisertib (TGFβ receptor inhibitor) and cap cetabine.

CONCLUSIONS AND RECOMMENDATIONS
The response to current targeted agents and immunotherapies in mCRC is highly dependent on driver genomic events. Treatment decisions based on molecular subtypes have evolved markedly in the recent years. Predictive biomarkers were initially developed under the “one marker, one drug” paradigm of precision medicine. The limited efficacy of BRAF inhibitors in early clinical trials of BRAFV600E-mutant mCRC indicated that the single-alteration perspective for matched therapies had substantial limitations. Our current knowledge on the complexity of CRC genome, clonal selection under treatment pressure, and adaptive activation of parallel signaling pathways on targeted treatment exposure supports the transition to a “multimarker, multidrug” model when making therapeutic decisions. This paradigm was applied to KRAS wild-type HER2-amplified mCRC, leading to substantial antitumor activity of double HER2 blockade. The refined hyperselection of candidates for EGFR mAbs beyond RAS and BRAF mutation testing is another example: tumors wild-type for several rare genomic mechanisms of primary resistance known to activate the MAPK signaling, such as HER2 and MET amplifications and kinase fusions, have the highest chances of clinical benefit.52 Finally, a deeper characterization of transcriptomic subtypes, encompassing tumor, stromal, and immune components, revealed convergent pathway dependencies that mandate a “multomics, multidrug” model for development of novel therapies. This future paradigm of precision medicine holds promise for rational immunotherapy combinations in molecularly defined microsatellite-stable mCRC subpopulations.

In conclusion, the potential benefits of multiplexed genotyping platforms in individual patients with mCRC have already been demonstrated, and the next logical step is to facilitate larger clinical trials with biomarker-driven therapies. However, many issues must be addressed before widespread adoption of NGS or gene expression signatures in clinical practice. These are our recommendations:

1. All patients with mCRC eligible to palliative therapy should be tested for oncogenic KRAS and NRAS mutations before EGFR-targeted drugs.
2. The high concordance rates between tissue and plasma sequencing suggest that ctDNA can be used as a substitute for standard RAS mutation detection
in tumor samples. The value of sequential ctDNA analysis after anti-EGFR therapy for the identification of targetable resistance mechanisms or a wild-type population eligible to EGFR mAb rechallenge is under investigation.

3. **BRAF**-V600E is a strong negative predictive marker for anti-EGFR benefit and should be assessed as early as possible in the evolution of the disease to guide sequential treatment decisions.

4. Universal MSI testing for all patients with personal histories of CRC could identify individuals with Lynch syndrome and inform the use of immunotherapy in patients with metastatic disease.

5. **HER2** amplification and overexpression tests are recommended in patients eligible to clinical trials with targeted agents, particularly those with microsatellite-stable RAS/BRAF wild-type tumors, left-sided primary tumors, and resistance to anti-EGFR therapies.

6. At reference institutions with access to experimental therapies, comprehensive genomic tests should be conducted to identify rare fusion events, known to be enriched in MSI right-sided tumors that are RAS/BRAF wild-type.

7. NGS for mutation burden quantification and DNA repair deficiency detection or gene expression profiling to identify oncogenic signatures of interest, such as “MSI-like” or mesenchymal phenotype, should be limited to research groups for which matched clinical trials are available.

We strongly believe that to optimize clinical outcomes in molecularly homogenous CRC populations, the evolution of clonal cancer cell events and interactions with tumor microenvironment should be taken into consideration. An integrative and dynamic classification system that links molecular features to targeted drugs and immunotherapies has the potential to revolutionize precision medicine in mCRC.

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**References**


Where We Stand With Immunotherapy in Colorectal Cancer: Deficient Mismatch Repair, Proficient Mismatch Repair, and Toxicity Management

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OVERVIEW

With the recent U.S. Food and Drug Administration approvals of pembrolizumab and nivolumab for refractory deficient mismatch repair metastatic colorectal cancer, immune checkpoint inhibitors have now entered into clinical care for gastrointestinal cancers. Extensive ongoing efforts are exploring additional combinations of therapy in both deficient and proficient mismatch repair colorectal cancer. This review will outline the current status of such efforts and discuss the critical aspects of recognition and management of immune-related toxicities from checkpoint inhibitors.

The discovery of immune checkpoints and their role in regulating host immune response to cancer has provided therapeutic targets for clinicians. Although there are now many recognized immune checkpoints, therapeutic antagonistic monoclonal antibodies have been developed for three targets (PD-1, its ligand PD-L1, and CTLA-4) and the U.S. Food and Drug Administration (FDA) has approved their use in a wide variety of cancers. The tremendous survival benefit seen from treatment with checkpoint inhibitors among many patients with cancer has led to the widespread adoption of checkpoint inhibitors in the clinic and the expansion of the field of immuno-oncology.

In gastrointestinal oncology, the first FDA-approved checkpoint inhibitors were pembrolizumab and nivolumab for the treatment of refractory deficient mismatch repair (dMMR) metastatic colorectal cancer (CRC). This represents approximately 4% of metastatic CRC, which is characterized by very high levels of mutations. Because these mutations are frequently seen at areas of DNA repeats or microsatellites, this deficiency in DNA MMR has also been termed microsatellite-instability high (MSI-H). With these approvals, a number of phase III clinical trials on dMMR CRC have initiated. However, single-agent checkpoint inhibitors have not demonstrated meaningful clinical activity for patients with proficient mismatch repair (pMMR) CRC. Extensive basic science and clinical trial efforts are underway to identify the optimal combinations that are needed for activity in the more common pMMR CRC subset.

With the recent incorporation of checkpoint inhibitors into gastrointestinal oncology, the recognition and management of immune-related toxicities is of great importance. Because these manifest in distinctly different ways from standard chemotherapy toxicities, understanding of these potential life-threatening toxicities is of critical importance to clinical practice.

This review discusses the recent changes in clinical care for patients with dMMR cancer and the ongoing research efforts for pMMR CRC and provides guidance for the recognition and management of immune-related toxicities.

UNDERSTANDING MISMATCH REPAIR AND MICROSATELLITE INSTABILITY

MMR is one of the many mechanisms that cells use to repair damaged DNA. In particular, MMR recognizes and repairs insertions, deletions, and mis-incorporations of DNA bases during DNA replication. As expected, deficiency in the MMR system leads to the accumulation of mutations. Thus, CRCs with dMMR have a markedly elevated tumor mutation rate, with one study demonstrating a mean mutation rate of 1,782 for dMMR CRC compared with 73 for pMMR CRC. These types of DNA errors, which are recognized and repaired by MMR, preferentially occur at areas of DNA repeats, termed microsatellites. Because of this association, patients with dMMR will demonstrate variation in the length of various microsatellites when comparing normal and tumor sequences and this is termed MSI-H. Deficiency or dysfunction of MMR proteins such as MLH1, MSH2, MSH6, PMS2, and TACSTD1/EPCAM will result in dMMR.

Identification of dMMR can be accomplished by immunohistochemical staining for the complete loss of one of the
four most common MMR proteins: MLH1, MSH2, MSH6, and PMS2. In addition, testing for variation in length of microsatellites can be used to diagnose dMMR. The classic testing for MSI-H is based on consensus guidelines that recommend the testing of five specific microsatellites (BAT25, BAT26, D2S123, D5S346, and D17S250) via polymerase chain reaction with the determination of MSI-H based on instability (length variation between tumor and normal) at greater than 30% of tested microsatellites. More recently, large-coverage next-generation sequencing panels have demonstrated the ability to identify patients with dMMR by evaluating variation at a large number of microsatellites across the genome. In one recent report evaluating the next-generation sequencing MSI identification algorithm termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC and termed “MSIsensor,” the specificity and sensitivity were 100% and 99.3%, respectively, for 178 patients with CRC. Given the strong concordance across the various dMMR/MSI-H methodologies, the FDA approvals for dMMR CRC, discussed below, were not based on a specific testing methodology.

Accordingly 15% of CRCs have dMMR; however, this rate decreases by stage, with approximately 4% of patients with stage IV disease demonstrating dMMR. Of patients with dMMR, Lynch syndrome or hereditary nonpolyposis CRC will be present in about one-third of patients. The remainder of patients will have dMMR from sporadic acquisition, most commonly from methylation of MLH1, resulting in loss of MLH1 protein expression, or from biallelic mismatch repair somatic mutations. At present, it is recommended that all patients with metastatic CRC undergo testing for dMMR to identify not only patients with Lynch syndrome but also patients who could be treated with anti–PD-1 therapy.

PRACTICAL APPLICATIONS

- All patients with colorectal cancer should undergo testing for microsatellite instability (mismatch repair) status.
- Checkpoint blockade therapy shows dramatic response rates and durability of response in MSI-H (dMMR) colorectal cancer and is currently approved by the FDA for MSI-H (dMMR) after fluoropyrimidine, oxaliplatin, and irinotecan.
- Because microsatellite-stable (proficient mismatch repair) colorectal cancer does not respond to single-agent checkpoint blockade, new strategies are evaluating combinations with chemotherapy, vaccines, depletion of myeloid-derived suppressor cells, and depletion of regulatory T cells.
- A high index of suspicion should be maintained for immune-related adverse events caused by checkpoint blockade, which can affect any organ system.
- Treatment of suspected severe immune-related adverse events is generally 1 mg/kg of prednisone or equivalent. Refractory autoimmunity may require additional immune modulators.

DEFICIENT MISMATCH REPAIR COLORECTAL CANCER

There has been a longstanding awareness of the unique immune tumor microenvironment of dMMR CRC with histopathology characterized by tumor-infiltrating lymphocytes and a Crohn-like lymphoid reaction. This robust immune response is likely responsible for the favorable outcome of patients with primary resected dMMR CRC. Based on this known immune recognition of dMMR CRC and the high mutation rate within these cancers, two clinical trials were initiated to explore anti–PD-1 therapy in advanced CRC.1,3-5

In the KEYNOTE 016 clinical trial, patients with pMMR CRC, dMMR CRC, and dMMR non-CRCs were enrolled and treated with single-agent pembrolizumab.1,5 The initial report of this study demonstrated response rates of 40% (4 of 10) and 78% (7 of 9) for patients with dMMR CRC and dMMR non-CRC, respectively, whereas the response rate was 0% (0 of 18) for patients with pMMR CRC. As expected, high somatic mutation loads were correlated with prolonged progression-free survival. Updated results from this trial were recently reported for 86 dMMR cancers. A total of 12 different tumor types were studied, with the most common tumor type being CRC (40 patients). The overall response rate was 53% (52% in patients with CRC and 54% in patients with non-CRC). Estimated 1- and 2-year progression-free survival was 64% and 53%, respectively. Patients treated per protocol stopped therapy at 2 years; of the 18 patients who stopped therapy, none have yet had a recurrence at a median follow-up of approximately 8 months. Such results suggest that the durability of clinical benefit seen with anti–PD-1 therapy in dMMR cancers may result in cures, although longer follow-up is needed. In May 2017, the FDA approved pembrolizumab for patients with dMMR CRC after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan and for dMMR solid tumors that do not have satisfactory alternative treatment options. This approval was based on the above-mentioned trial plus prospective and/or retrospective analyses of patients with dMMR from four additional trials. In total, 149 patients with dMMR (90 with CRC and 59 with non-CRC) demonstrated an overall response rate of 39.6%, with similar response rates in the CRC cohort (36%) as the non-CRC cohort (46%).

In July 2017, the FDA also approved nivolumab for patients with dMMR CRC after prior treatment with fluoropyrimidine, oxaliplatin, and irinotecan based on results from the CheckMate 142 study.1,4 In total, 74 patients with dMMR CRC were treated with single-agent nivolumab.3 The overall response rate was 31.1%, with 69% of patients demonstrating disease control for 12 weeks or longer. Twelve-month progression-free survival was 50% and 12-month overall survival was 73%. In addition to this single-agent nivolumab cohort, the CheckMate 142 study also explored the combination of nivolumab plus ipilimumab for a nonrandomized concurrently enrolled cohort of 119 patients with dMMR CRC.4 The combination of nivolumab and ipilimumab demonstrated improved outcomes with an overall response rate of 55%, 12-month progression-free survival of 71%,
and 12-month overall survival of 85%. Grade 3 to 4 treatment-related adverse events occurred for 32% of patients, whereas this rate was 20% in the single-agent nivolumab cohort. These results, suggesting additional clinical benefit with a combinatorial approach for dMMR CRC, have laid the groundwork for the exploration of additional combination therapies in dMMR cancers.

At present, a number of phase III clinical trials are underway that explore the use of anti–PD-1 or anti–PD-L1 therapy in dMMR CRC (Table 1). Two clinical trials are exploring the use of pembrolizumab or atezolizumab in the first-line metastatic setting and one clinical trial is exploring the use of atezolizumab in combination with folinic acid, fluorouracil, and oxaliplatin as adjuvant therapy for stage III dMMR CRC.

**PROFICIENT MISMATCH REPAIR COLORECTAL CANCER**

The impressive rates and durability of tumor regression and disease control experienced by patients with CRC with dMMR/MSI-H disease treated with anti–PD-1 therapy stand in stark contrast to the lack of response experienced by those with pMMR/microsatellite stable disease as described above. Therefore, one approach to developing immunologic treatments for pMMR CRC first seeks to understand the differences in tumor molecular patterns, immune cell content, and cytokine expression between dMMR and pMMR CRC that renders dMMR tumors responsive to immune manipulations and then attempts to replicate these favorable conditions within pMMR CRC (in other words, altering the pMMR CRC to be more dMMR like). As described above, it has long been appreciated that an increased immune infiltrate accompanies dMMR CRC. Indeed, the presence of an antitumor T-cell infiltrate appears to be critical to the activity of PD-1/PD-L1 blockade. So too in unselected CRC (mostly pMMR), the extent of T-cell infiltrate correlates with improved outcome. More recently, gene expression profiling has confirmed these findings. Comparing differential gene expression in primary dMMR and pMMR CRCs, Mlecnik et al observed that many of the differentially regulated genes were related to immune system activities. Analysis of the immunome, the gene patterns that identify 28 different immune cell types, confirmed the higher expression of genes descriptive of CD8+ cytotoxic and CD4+ T-helper 1 cell types. Immunostimulatory cytokines and chemokines such as interferon-gamma, interleukin-15, GNYL, CCL3, and CXCL16 were increased, whereas others such as CXCL14, which is chemotactic for monocytes, were decreased in patients with dMMR. Interestingly, some pMMR tumors with profiles similar to dMMR tumors (high T-helper 1 cells, cytotoxic genes, cytokines, and chemokines) have a prognosis similar to dMMR malignancies and notably better than for pMMR tumors without these profiles. Therefore, it is possible for pMMR CRC to have a dMMR-like immune phenotype; however, whether these dMMR-like pMMR CRCs will experience responses to checkpoint blockade or any other immunotherapy that mirrors the clinical responses of dMMR CRC is unknown. Nonetheless, this hypothesis, that creating a T-cell–infiltrated environment would increase the immune responsiveness of pMMR CRC to checkpoint blockade, is at the heart of recent “blueprints” for bringing immunotherapy to the majority of patients with CRC.

The most striking genomic explanation underlying the different immune response patterns of dMMR and pMMR tumors is the much higher frequency of neoantigens available in dMMR tumors as a result of their high mutational burden. The neoantigen load is correlated with the extent of tumor-infiltrating lymphocytes in CRC, not only among dMMR and POLE exonuclease domain–mutated CRC (also having high neoantigen loads) but also among pMMR. Although there is not a strict cutoff for neoantigen load associated with increased T-cell infiltration, it does appear that the neoantigen load associated with marked T-cell infiltration is well above that seen in most microsatellite stable/POLE wild-type CRC. Therefore, it is likely that other strategies to enhance T-cell infiltration, particularly the memory CD45RO+ T cells, into pMMR tumors with lower mutational burden will be required. Furthermore, the greater presence of immunoinhibitory cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells within pMMR tumors may explain the poor immune response to pMMR CRC.

The remainder of this section will focus on strategies under development to enhance effector T-cell activation and infiltration into CRCs and decrease the immune-inhibitory cell population.

Although pMMR CRCs may have lower mutational and neoantigen burden, they do harbor some mutated proteins against which T-cell responses have been identified (e.g., mutated KRAS or p53) and also express cancer germ-line antigens to which immune tolerance would not have developed. Furthermore, tumor-infiltrating lymphocytes from pMMR CRC recognizing tumor antigens have been isolated. The very presence of these T cells, albeit at very low frequency prior to any therapy, highlights the ability of the activation phase of the cancer immunity cycle in which dendritic cells acquire and process tumor antigens shed from dying tumor cells and present them within surface-expressed major histocompatibility complex (HLA) molecules to prime antigen–specific CD4+ and CD8+ T cells. Therefore, there has been considerable interest in developing strategies to target an immune response against the antigens displayed by the malignancy alone or in conjunction with checkpoint blockade.

Therapies that destroy tumors (chemotherapy, radiotherapy, and targeted therapies) and thereby release tumor antigen represent the most straightforward strategy for combination with checkpoint blockade and other immunotherapies. These standard therapies, far from impairing immune responses as once feared, may also enhance immune activation. Radiotherapy induces immunogenic cell death, activation of tumor-associated dendritic cells and effector lymphocytes, and increased intratumoral T-cell infiltration and has repeatedly been reported to cause an abscopal effect on metastatic cancers. Chemotherapy also induces immunogenic cell death, and it has been established in lung cancer that increased clinical activity may be seen with
### TABLE 1. Clinical Trials Investigating Immune Therapy in Colorectal Cancer

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Agent</th>
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<td>COTEZO IMblaze370 (NCT02788279)</td>
<td>Cobimetinib with atezolizumab, atezolizumab monotherapy vs. regorafenib</td>
<td>PD-L1 Mek</td>
<td>Refractory metastatic CRC (dMMR limited; pMMR)</td>
<td>III</td>
</tr>
<tr>
<td>CheckMate 142 (NCT02060188)</td>
<td>Nivolumab/ipilimumab/drug: cobicetinib or daratumumab or anti-LAG-3 antibody</td>
<td>PD-1 CTLA-4 Lag3 MEK CD38</td>
<td>Pretreated metastatic CRC pMMR and dMMR</td>
<td>II</td>
</tr>
<tr>
<td>CheckMate 9N9 (NCT03377361)</td>
<td>Nivolumab/trameztinib with or without ipilimumab</td>
<td>PD-1 CTLA-4 MEK</td>
<td>Pretreated metastatic CRC (MMR not specified)</td>
<td>I/II</td>
</tr>
<tr>
<td>NCT03271047</td>
<td>Binimetinib with nivolumab with or without ipilimumab</td>
<td>PD-1 CTLA-4 MEK</td>
<td>Pretreated metastatic CRC pMMR mutated RAS</td>
<td>I/II</td>
</tr>
<tr>
<td>NCT03256344</td>
<td>Talimogene laherparepvec with atezolizumab</td>
<td>PD-L1</td>
<td>Liver metastases of CRC</td>
<td>I</td>
</tr>
<tr>
<td>NCT03182894</td>
<td>Epacadostat with pembrolizumab with azacitidine</td>
<td>PD-1 IDO</td>
<td>Metastatic CRC MSS</td>
<td>I II</td>
</tr>
<tr>
<td>NCT02777710</td>
<td>Durvalumab plus CSF-1R TKI (pexidarotinib)</td>
<td>PD-L1 CSF-1R</td>
<td>Refractory metastatic CRC</td>
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</tr>
<tr>
<td>NCT02559024</td>
<td>Anti-OK40 antibody (MEDI6469)</td>
<td>OX-40</td>
<td>Liver metastases of CRC</td>
<td>I</td>
</tr>
<tr>
<td>NCT03081494</td>
<td>PDR001/regorafenib</td>
<td>PD-1</td>
<td>Metastatic CRC pMMR</td>
<td>IB</td>
</tr>
<tr>
<td>QUILT-3.050 (NCT03169777)</td>
<td>Avelumab, bevacizumab, capecitabine, cetuximab, cyclophosphamide, 5-fluorouracil, fulvestrant, leucovorin, nab paclitaxel, nivolumab, omega-3-acid ethyl esters (Lovaza; Teva, North Wales, PA), oxaliplatin, stereotactic body radiation therapy, ALT-803, ETBK-011, ETBK-021, ETBK-051, ETBK-061, GI-4000, GI-6207, GI-6301, and haNK</td>
<td>Numerous</td>
<td>Metastatic CRC MMR not specified</td>
<td>IB/II</td>
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Continued
Table 1. Clinical Trials Investigating Immune Therapy in Colorectal Cancer (Cont'd)

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Agent</th>
<th>Target</th>
<th>Study Population</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02834052</td>
<td>Pembrolizumab/poly-ICLC</td>
<td>PD-1, TLR3</td>
<td>Pretreated metastatic CRC pMMR</td>
<td>I/II</td>
</tr>
<tr>
<td>NCT02650713</td>
<td>TCB CEA (RO6958688) plus atezolizumab</td>
<td>PD-1, CEA</td>
<td>Metastatic cancers</td>
<td>I/II</td>
</tr>
</tbody>
</table>

Abbreviations: dMMR, deficient mismatch repair; CRC, colorectal cancer; FOLFIR, folic acid, fluorouracil and oxaliplatin; pMMR, proficient mismatch repair; CRC, mismatch repair; Ad, adenovirus; CEA, carcinoembryonic antigen; PD-L1, PD-L2, PD-L3, and indinavir; GM-CSF, granulocyte-macrophage colony-stimulating factor; IDO, indoleamine 2,3-dioxygenase; MSS, microsatellite stable; TKI, tyrosine kinase inhibitor; hNK, high affinity natural killer cells; TCB, T-cell bispecific.

Chemotherapy plus checkpoint blockade, supporting similar testing in other malignancies. Several early and later-line studies testing chemotherapy plus anti–PD-1 or anti–PD-L1 or radiotherapy delivered as external beam or as radioembolization (Table 1) are ongoing in metastatic CRC. Other therapies that are standard for CRC, such as anti-EGFR therapy with cetuximab and anti-VEGF therapy with bevacizumab, may have synergy with immune therapies as well (bevacizumab by reducing the levels of free VEGF, which has immunoinhibitory effects, and cetuximab by activating antibody-dependent cellular cytotoxicity).19

An alternative approach to activating an immune response against the tumor antigens is the intratumoral or intravenous administration of replication competent oncolytic viruses, often modified to express immunomodulatory genes, that are capable of infecting and lysing malignant cells thereby releasing antigen. In the resulting inflammatory milieu, innate immune responders such as dendritic cells infiltrate and acquire, process, and present antigen to T cells. Chaurasiya and Warner20 reviewed the preclinical and clinical status of this so-called viroimmunotherapy in CRC; in brief, leading viruses include oncolytic Ad11/Ad3 chimeric group B adenovirus, Newcastle disease virus, vaccinia, herpesvirus, and reovirus, which have reported preliminary results from earlier phase studies.

Cancer vaccines seek to activate CD4 and CD8+ T cells against tumor antigens by supplying them in a context where a potent T-cell response may be activated. These vaccines may be based on peptides and proteins mixed with immunostimulatory adjuvants, viral vectors encoding tumor antigen, modified tumor cells, and antigens delivered with autologous dendritic cells.21 Vaccines targeting known overexpressed or mutated tumor antigens have activated T-cell responses against those antigens in patients with CRC.22 Although cancer vaccines alone have had modest activity, best observed in the setting of minimal disease,23 preclinical data suggest that in combination with checkpoint blockade, they are able to increase CD8+ T-cell infiltration into the tumor with a concomitant decrease in Tregs.24 Current clinical trials are combining CRC vaccines with chemotherapy and/or checkpoint blockade or stimulators of innate immunity signaling through Toll-like receptors such as poly-ICLC or MGN1703 or through cyclic dinucleotides (Table 1).

Downregulation of antigens, major histocompatibility complex molecules, and immunostimulatory cytokines has been observed in tumors exposed to immune attack and it has been proposed that epigenetic regulation may account for this. Epigenetic modulators may upregulate immunomodulatory pathways, tumor antigens, major histocompatibility complex proteins, and interferons and synergize with standard immunotherapies.25,26 The combination of epigenetic modifiers and checkpoint blockade is in clinical trials for CRC (Table 1).

Other strategies to target tumor antigens include bispecific T-cell–engaging antibodies that simultaneously bind T cells and tumor cells and chimeric antigen receptor T cells. Specific T-cell–engaging antibodies that simultaneously bind antibody-dependent cellular cytotoxicity.19 Such approaches result in a large number of T cells capable of recognizing and attacking tumor cells. Preclinical data support the combination of bispecific T-cell–engaging antibody molecules targeting carcinoembryonic antigen on tumors and CD3 on T cells with anti–PD-1 or anti–PD-L1.27 The T-cell bispecific carcinoembryonic antigen, in a phase I study alone or in combination with atezolizumab, demonstrated increased T-cell infiltration and clinical responses but also a high rate of infusion reactions, fever, and diarrhea.28 This study is continuing to recruit patients (Table 1).

The observation that pMMR CRCs are infiltrated with myeloid-derived suppressor cells and Tregs suggests that greater immunity could be achieved by depleting these cell types. Preclinical data in a mouse model of colon adenocarcinoma demonstrated that an anti-CSF1R antibody could delay tumor growth, associated with a decrease in myeloid-derived suppressor cells. Other preclinical studies have shown synergy between this CSF1R targeting and checkpoint blockade.29,31 A recent clinical trial has combined nivolumab with the anti-CSF1R antibody cabiralizumab,32 although it is being pursued now in pancreatic cancer; however, the CSF-1R tyrosine kinase inhibitor pexidarstered is being combined with durvalumab in CRC (Table 1). The observation that KW-0761 (mogamulizumab) depletes CCR4+ inhibitory Tregs in patients with cancer33 has opened the possibility that it could be used in combination with other immune therapies for malignancies highly infiltrated with Tregs. The immunosuppressive effect of high IDO, an enzyme that metabolizes tryptophan into kynurenine, depriving T cells of tryptophan and suppressing them through kynurenine's effects on dendritic cells, is associated with outcome in CRC.34 The IDO inhibitor epacadostat has been evaluated in advanced cancers in combination with pembrolizumab and a study in CRC is anticipated to begin in early 2018 (Table 1). Adenosine, generated from adenosine triphosphate by CD73 in the tumor microenvironment, has immunosuppressive
effects through the A2A adenosine receptor expressed by immune cells, specifically, inhibiting T-cell and natural killer T-cell proliferation and enhancing proliferation of Tregs and myeloid-derived suppressor cells. Anti-CD73 antibody alone and with checkpoint blockade had activity in murine CRC models and anti-CD73 antibody MEDI-9447 is in clinical trials with durvalumab, although it is being studied in lung cancer. Finally, just as the deployment of other checkpoint molecules within the tumor microenvironment or lack of immune agonists may explain resistance to checkpoint blockade in dMMR CRC, it is possible that one of the checkpoints under study, such as TIM-3 or LAG-3, as well as immune agonists including GITR, OX40, 4-1BB, CD40, ICOS, or CD27 may also require modulation in pMMR CRC. Supportive preclinical data have been generated for some of these approaches.

Although the MAPK pathway plays an important signaling role in CRC, it has also been observed that MEK inhibitors can modulate antitumor immunity by increasing HLA expression and T-cell infiltration into tumors. In a study of the anti–PD-L1 antibody atezolizumab in combination with a MEK inhibitor, cobimetinib, including pMMR CRC, initial reports suggested an overall response rate of 17% (four with a partial response, and five with stable disease), but a more recent presentation noted that the rate decreased to 8%. Nonetheless, survival was as high as 13 months among those with confirmed pMMR CRC. The results of a pivotal trial of this approach are pending (Table 1) and other MEK inhibitor/checkpoint blockade combinations are under study. PI3K pathway activation as a result of alterations such as loss of PTEN and PIK3CA mutations is frequently identified in CRC and this pathway activation is associated with checkpoint upregulation. Therefore, PI3K pathway inhibition combined with checkpoint blockade is also under evaluation.

MANAGEMENT OF IMMUNE-CHECKPOINT TOXICITY

With the expanded use of checkpoint inhibitors have come growing understandings of their unique scope of toxicities that differ in characteristics, presentation, onset, severity, and treatment from previously commonly used cancer therapeutics. Toxicities are related to the unique checkpoint inhibitor mechanism of action that is shared by this class of agents (i.e., “unleashing” of the immune brakes and subsequent activation of self-directed T cells and autoantibodies as well as the cascade of cytokines that mediated development of autoimmunity). Immune-related adverse events (irAEs) span all organ systems (Table 2) and their clinical presentation ranges from asymptomatic biochemical or radiologic changes, to insidious onset of symptoms, to symptoms that are rarely explosive in nature. Thus, the challenge for oncologists as well as primary care providers and other subspecialists is to recognize these syndromes and to assess their severity and the need for intervention by withholding therapy and initiating immune suppression. Depending on the irAE and the agent, checkpoint inhibitors may be reinitiated following resolution of the adverse event.

The importance of recognizing and managing irAEs from these agents has been recognized by the major international and national societies and groups with comprehensive review articles and guidelines from the Society of Immunotherapy for Cancer, the European Society for Medical Oncology, ASCO, and the National Comprehensive Cancer Network (unpublished data, 2018). In addition, to reach the nononcologic community, a separate review was published in the New England Journal of Medicine in January 2018. For a complete review of the topic of irAEs, we refer readers to the above-referenced publications.

Adverse events to checkpoint inhibitors vary across the severity scale, with most patients having low-grade (grade 1 or 2) symptoms that may be attributable to immune-related events. These include anemia, lymphopenia, pruritus, rash, diarrhea, dry mouth, elevated liver and pancreatic enzymes, arthralgia, myalgia cough, dyspnea, low-grade fever, and fatigue. Low-grade skin toxicity with rash or pruritus is the most frequently observed, with vitiligo noted for patients with melanoma for the most part. Diarrhea is the next most frequent. Toxicities are more frequent with anti–CTLA-4 inhibition; anti–PD-1 checkpoint inhibitors have slightly more side effects than those observed with anti–PD-L1 checkpoint inhibitors.

Severe grade 3 or 4 irAEs are more frequently seen with anti–CTLA-4 checkpoint inhibitors and appear to be dose related. Grade 3 or 4 diarrhea predominates in anti–CTLA-4 checkpoint inhibitors, with endocrine-related toxicity being the next most common irAE. Clinicians should be alerted that multiple irAEs can occur synchronously or metachronously.

Although most irAEs occur in the 3 to 6 months after initial treatment, they may occur following the first dose and, rarely, can be delayed by months to even years after completion of treatment. Awareness of the clinical presentation with appropriate clinical investigation to determine the etiology remains the bedrock of surveillance and treatment. Evaluation of any irAE should include consideration of other potential causes such as infection, other medication, or cancer progression.

Once recognized, management of grade 1 to 2 toxicities typically requires appropriate supportive care and continuation of checkpoint inhibitors with close observation to ensure that the toxicity does not progress to grade 3 or 4. Grade 3 or 4 toxicities require interruption of the therapy and treatment with immune-suppressive agents. High-dose glucocorticoids are the first-line therapy, with 1 to 2 mg/kg of prednisone or its equivalent initiated for approximately 2 to 4 weeks prior to tapering. Prophylactic antibiotics for prevention of Pneumocystis pneumonia should be used for prolonged steroid use. Hospitalization and intravenous therapy is required for patients who have difficulty with oral glucocorticoid treatment or concerns regarding gastrointestinal absorption. Intravenous fluid replacement for severe diarrhea may also be required.

Typically, irAEs resolve rapidly within 1 week following glucocorticoid initiation. For patients who do not respond,
additional immune suppression with mycophenolate or infliximab must be considered. Mycophenolate is the preferred second-line treatment for immune-related hepatitis. Although the majority of patients with irAEs recover completely, the endocrine changes are frequently permanent and other chronic irAEs are observed (e.g., colitis and arthritis) that warrant ongoing immune suppression.

There are rare irAEs that warrant special attention. Myocarditis is reported for approximately 0.3% of patients and presents with arrhythmias or signs and symptoms of cardiac failure and cardiac muscle damage with elevation in troponin. There is a high mortality rate associated with myocarditis; thus, hospitalization, close monitoring, and initiation of glucocorticoids and infliximab are warranted. Severe myositis can also be seen and if unrecognized may lead to rhabdomyolysis. Clinicians should also be aware of the precipitous development of type 1 diabetes and patients presenting with diabetic ketoacidosis. Notable elevations in serum

| TABLE 2. Frequency of Checkpoint Inhibitor–Related Toxicity by Organ System |
|-------------------------------|-------------------------------|
| **Organ/System**              | **Syndrome**                  | **Frequency (%)** |
| Skin                          | Maculopapular rash            | Approximately 30–50 |
|                               | Pruritus                      |                   |
|                               | Vitiligo (melanoma)           |                   |
|                               | Bullous disease               |                   |
|                               | Stevens-Johnson/toxic epidermal necrolysis syndromes | |
| Gastrointestinal              | Colitis                       | Approximately 20–40 |
|                               | Gastritis                     |                   |
|                               | Ileitis                       |                   |
| Liver                         | Hepatitis                     | Approximately 4–15 |
| Endocrine                     | Hypothyroidism                | Approximately 10–50 |
|                               | Hyperthyroidism               |                   |
|                               | Hypoadrenalinism              |                   |
|                               | Hypophysis                    |                   |
|                               | Type 1 diabetes               |                   |
| Pulmonary                     | Pneumonitis                   | Approximately 1–5 |
|                               | Sarcoidosis                   |                   |
| Musculoskeletal               | Arthralgia                    | Approximately < 1–15 |
| Rheumatologic                 | Arthritis                     |                   |
|                               | Myositis                      |                   |
|                               | Sjögren syndrome              |                   |
| Cardiac                       | Myocarditis                   | Approximately < 1 |
|                               | Pericarditis                  |                   |
| Hematologic                   | Anemia                        | Approximately < 1–5 |
|                               | Lymphopenia                   |                   |
|                               | Thrombocytopenia              |                   |
|                               | Post-treatment lymphocytosis, eosinophilia, neutrophilia | |
| Renal                         | Nephropathy                   | Approximately < 2–30 |
| Neurologic                    | Posterior reversible encephalopathy | Approximately < 4–15 |
|                               | Guillain-Barré syndrome       |                   |
|                               | Peripheral neuropathy         |                   |
|                               | Myasthenia gravis             |                   |
|                               | Aseptic meningitis            |                   |
|                               | Transverse myelitis           |                   |
| Ophthalmologic                | Uveitis                       | Approximately 1 |
|                               | Episcleritis                  |                   |
|                               | Voght-Koyanagi-Harada disease |                   |
|                               | Conjunctivitis                |                   |
glucose from baseline should prompt evaluation for ketones and the development of diabetes. Although episcleritis, conjunctivitis, and uveitis are noted, special precautions should be given to eye symptoms and signs, because the clinical severity may not reflect the serious development of panuveitis, ocular sarcoid syndrome, and Vogt-Koyanagi-Harada syndrome, which, if untreated, can lead to blindness. Checkpoint inhibitor–induced pneumonitis can masquerade as infection on radiographs or CT scans and be asymptomatic, requiring no immediate therapy but close follow-up, or can progress to pulmonary failure and death if untreated with immune suppression.

At this time, the empirical data suggest that patients who develop grade 3 to 4 irAEs to Checkpoint inhibitor therapy requiring immune suppression therapy continue to have similar benefits compared with patients who do not require immune suppression therapy. Reinitiation of anti–PD-1 or anti–PD-L1 therapy following grade 3 to 4 irAEs related to these agents can be safely achieved for approximately 50% of patients; recurrence of the same irAE or other irAEs is seen for the other 50%. Patients with serious irAEs attributable to CTLA-4 or an anti–PD-1 plus anti–CTLA-4 combination checkpoint inhibition can typically continue taking an anti–PD-1 following resolution of their irAEs.

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GASTROINTESTINAL (NONCOLORECTAL) CANCER
What Will We Expect From Novel Therapies to Esophageal and Gastric Malignancies?

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OVERVIEW

Esophageal cancer and gastric cancer are aggressive diseases for which treatment approaches are facing a new era. Some molecular pathways, such as VEGF, EGFR, fibroblast growth factor receptor, PIK3CA, and PARP-1, have been studied, and novel targeted drugs are presumed to be developed in the near future. From The Cancer Genome Atlas report, 80% of Epstein-Barr virus tumors and 42% of tumors with microsatellite instability have PIK3CA mutations, suggesting that this pathway could be reevaluated as a possible target for new systemic treatment of gastric cancer. Notably, higher PARP-1 expression can be found in gastric cancer, which might be related to more advanced disease and worse prognosis. In addition, PD-L1 expression, high microsatellite instability, and mismatch repair deficiency can be found in gastric cancer, thus suggesting that immunotherapy may also play a role in those patients. We discuss trends related to the potential of novel therapies for patients with esophageal and gastric cancers in the near future.

The relative prevalence of gastric cancer has decreased over the past few decades, from the leading cause of cancer in 1975 to the fifth most common cancer; it is also the third leading cause of cancer-related death in both sexes worldwide.1,2 Gastric cancer is also the leading cancer associated with infection,3 due to Helicobacter pylori and Epstein-Barr virus (EBV). Gastric cancer has a twofold greater incidence in men than women and heterogeneous distribution across the world, with higher incidence and mortality rates in Asian countries, such as Korea, Japan, and China, and the lowest incidence in the Western world, such as in North America, where it is one of the least common cancers.3,5 Southern Europe, where this disease is the sixth most common malignancy, is also considered a high-risk area.6 Some risk factors that are associated with the development of gastric cancer include high intake of processed red meat or smoked preserved foods, smoking, high alcohol intake, and Helicobacter pylori infection, which is the main cause of noncardia gastric cancer; however, few studies have been conducted in low-income countries with high gastric cancer incidence.7 Histologically, gastric adenocarcinomas are classified as intestinal (85%–90%) or diffuse (10%–15%). The majority of gastric adenocarcinoma cases are sporadic (90%–95%), and only 5% to 10% have familial predisposition. Anatomically, proximal tumors are more common in Western countries, and nonproximal tumors are more frequent in Asian countries.6 By the American Joint Committee on Cancer staging system, proximal stomach tumors crossing the esophagogastric junction are classified and treated as esophageal carcinomas.8

MOLECULAR CLASSIFICATION

Traditionally gastric cancers are classified into intestinal and diffuse histologic subtypes, the so-called Lauren classification, although mixed subtypes are reported as well.9 Comprehensive analysis of driver mutations in gastric cancer has revealed that a multitude of genes are causally involved in cancer development and progression, including TP53, ARID1A, PIK3CA, and RHOA.10-12 Some of these mutations associate with a specific type of gastric cancer; for example, RHOA mutations are largely confined to diffuse-type gastric cancer. Additional genetic aberrations involve amplifications of genes including ERBB2, FGFR2, MET, and KRAS, resulting in activation of pathways downstream the receptor tyrosine kinases and RAS signaling, providing leads for targeted therapy (see below). However, as in other cancer...
types, responses to single targeted agents are often disappointing, suggesting additional complexity and the need for additional biomarkers.

In a key publication, The Cancer Genome Atlas (TCGA) project proposes the division of gastric cancer into four genetically defined molecular subtypes: tumors positive for EBV (with recurrent PIK3CA mutations, extreme DNA hypermethylation, and amplification of JAK2, PD-L1, and PD-L2), tumors with microsatellite instability (MSI), genomically stable tumors, and tumors with chromosomal instability (i.e., with marked aneuploidy and focal amplification of receptor tyrosine kinases). To integrate not only genomic aberrations but also epigenetic modifications and microenvironmental heterogeneity, including properties of the immune infiltrate and activation state of the stroma, comprehensive gene expression–based classifications have been developed. The initial studies focused on gene expression profiles associating with intestinal and diffuse gastric cancer. Tan et al used representative cell lines to construct profiles that could discriminate the two gastric cancer types on the basis of gene expression data. This distinction also had predictive relevance, as cell lines representing the intestinal type were mostly oxaliplatin responsive, whereas diffuse gastric cancer lines were more responsive to cisplatin. Later this work was expanded to the detection of three subtypes: a proliferative type, a metabolic type, and a mesenchymal type. Also here distinct subtypes responded differently to therapeutic interventions: gastric cancers of the mesenchymal subtype were sensitive to PIK3CA, AKT, and mTOR inhibitors, and metabolic gastric cancers showed specific sensitivity to fluorouracil.

More recently, the Asian Cancer Research Group (ACRG) proposed another classifications on the basis of gene expression comprising four subtypes: a microsatellite-instable type, a mesenchymal-like type, and p53-active and p53-inactive types. The clinical relevance of these classifications is best studied for the TCGA or ACRG taxonomies. Regarding the TCGA classification, the EBV subtype was associated with the best prognosis, followed by microsatellite-instable and chromosomal-instability subtypes; the genomically stable subtype was associated with the worst prognosis. The ACRG classification scheme was also shown to be prognostic in several cohorts, as the microsatellite-instable subtype was associated with good prognosis and the mesenchymal-like type with poor disease outcome. Indeed, the identification of these subtypes (on the basis of TCGA or ACRG classification) might be useful for clinical decisions, prognostics, and research of new target therapeutics. Chromosomally unstable tumors represent 50% of all gastric cancers. Analysis of these tumors can reveal some recurring gene amplifications, such as HER2, EGFR, MET, CCNE1, CCND1, CDK6, VEGFA, and FGFR2, which are potentially targetable. The high-MSI subgroup corresponds to 22% of gastric cancers and is characterized by elevated mutation and hypermethylation rates, a median age of 72, and a higher proportion of females (56%). Higher mutation rates increase the likelihood of neoantigens, and therefore, high-MSI gastric cancer is a possible target for immune oncology. Genomically stable tumors represent 20% of gastric cancers, and some genetic changes can be found, such as RHOA signaling mutations, CLDN18-ARHGAP26 fusion, and fibroblast growth factor receptor (FGFR) 2 and VEGFA amplification. The EBV subtype is more common in fundus or body cancers and in men (81%), and it represents 9% of all gastric cancers and is characterized by high levels of DNA promoter hypermethylation, elevated expression of PD-L1 and PD-L2, JAK2 amplification, and PIK3CA mutation. Thus, the high expression of PD-L1 and PD-L2 raises the potential for immune therapy in this subgroup, as well as in the high-MSI subgroup. JAK-2 amplification and PIK3CA mutations are also possible targets for these patients (Fig. 1).

TREATMENT

In 2017, gastric cancer represented 1.7% of all cancer cases in the United States (with 28,000 new cases each year), with 5-year relative survival rates of 67.2% for localized disease, 30.7% for regional disease, and 5.2% for distant disease. Approximately 50% of patients with gastric cancer will be diagnosed with advanced-stage disease, but in some countries, such as Japan and South Korea, where screening is routinely performed, early detection is more frequent. The 5-year overall survival (OS) duration of metastatic gastric cancer might range from 3 months with only supportive care treatment to 16 months in fit patients in clinical trials; thus, gastric cancer is still an unmet need in oncology. In many Western countries, there is considerable overlap between gastric cancer and distal esophageal cancers in their treatment and clinical trial inclusion. In the United States, esophageal cancer is the fifth most common gastrointestinal cancer, with an estimated 16,940 new cases per year, and it is the sixth...
most common cancer worldwide.\(^{21}\) Approximately half of patients diagnosed with esophageal cancer present with unresectable or metastatic disease. Treatment of these patients aims to control dysphagia and other cancer-related symptoms, improve quality of life, and prolong survival. In the past 2 decades, modestly improved outcomes have been achieved in the treatment of patients with inoperable nonmetastatic cancer who are medically not fit for surgery or have unresectable, locally advanced disease. In distant metastatic esophageal cancer, several double-agent or triple-agent chemotherapy regimens have been established as first-line treatment options. Furthermore, long-term results of multiple large randomized phase III trials using additional targeted therapies have been published in the past few years, affecting contemporary clinical practice and future research directions.\(^{21}\) Here, we discuss the potential of further therapeutic directions and biomarkers for esophageal cancer and gastric cancer (EGC) in the advanced stage.

How Do We Treat Advanced EGC Today?

Today, treating advanced EGC is a difficult challenge for oncologists worldwide. Chemotherapy regimens, including different combinations of platinum, fluoropyrimidine, taxanes, and anthracyclines, were accepted as the backbone of first-line treatment of advanced disease.\(^{22,23}\) However, some other targeted therapies have been incorporated in this framework in recent years. For patients with advanced HER2-positive gastric cancer, researchers have found a great benefit in adding trastuzumab to platinum-fluoropyrimidine chemotherapy regimens.\(^{24}\) In addition, ramucirumab, in monotherapy or in combination with paclitaxel, an antiangiogenic monoclonal antibody, was approved for metastatic gastric cancer second-line treatment on the basis of results from the RAINBOW and REGARD phase III clinical trials.\(^{25,26}\) The tyrosine kinase inhibitor (TKI) apanitib, a drug against VEGFR-2, has demonstrated some benefit in patients with chemotherapy-refractory advanced or metastatic gastric cancer, becoming a possible third- or further-line treatment.\(^{26}\) Despite the aforementioned issues, the role of targeting therapies in gastric cancer is still limited. However, further research in this field could contribute to more clinical utility for the types of treatment of patients with gastric cancer.

Emerging Targets and Treatments

**HER2.** HER2 overexpression in gastric cancer ranges from 9% to 23% and is more frequent in the intestinal subtype; its prognostic value remains unclear, but HER2 should be tested in all patients with metastatic gastric cancer, using an immunohistochemistry-modified scoring system.\(^{27}\) After outstanding results in breast cancer, different clinical trials have targeted HER2, with different combinations of monoclonal antibodies, such as trastuzumab, pertuzumab, TDM-1, or the TKI lapatinib combined with chemotherapy or radiotherapy (RT). Thus, there are still many potential clinical benefits of different targeting combinations for HER2-positive disease. Currently, there are more than 118 trials on HER2-positive gastric cancer registered at ClinicalTrials.gov. See Table 1 for some relevant trials considered by our group. In 2017, Doi et al\(^{28}\) published an interesting phase I study addressing the safety and tumor activity of trastuzumab deruxtecan, an HER2-targeting antibody-drug conjugate, in patients with advanced breast and gastric or gastroesophageal tumors. Doi et al assessed 23 patients, of whom 10 (43%) had an objective response rate and 21 (91%) achieved disease control. The most common grade 3 and grade 4 toxicities were decreased lymphocyte
count, decreased neutrophil count, and anemia. Trastuzumab deruxtecan therefore shows important tumor activity in those tumors harboring HER2 overexpression. Further phase II and III trials are warranted to investigate the role of this drug in patients with EGC.28

Unlike breast cancers, however, the results of targeting HER2 in EGC have not been consistently positive. Recently, the JACOB trial (NCT01774786) treated 780 patients with HER2-positive metastatic or locally advanced unresectable GEJ cancer or gastric cancer with first-line trastuzumab and chemotherapy with or without pertuzumab. Unfortunately, this trial did not show any benefit in OS for patients treated with the combination of pertuzumab, trastuzumab, and chemotherapy compared with trastuzumab, chemotherapy, and placebo, with OS duration of 17.5 months compared with 14.2 months, respectively (HR 0.84; 95% CI, 0.71–1.00; p = 0.0565).40 Additionally, the TRIO-013/LOGIC and TyTan trials involved 545 patients. The median OS in the lapatinib and placebo arms was 12.2 months (95% CI, 10.6–14.2 months) and 10.5 months (95% CI, 9.0–11.3 months), respectively, which was not significantly different (HR 0.91; 95% CI, 0.73–1.12). Although there were negative results from the TRIO-013/LOGIC and TyTan trials,35,38 there are other trials of lapatinib therapy for HER2-positive gastric cancer that could be promising, such as MAGIC-B, which tested the addition of lapatinib or bevacizumab to perioperative chemotherapy with epirubicin, cisplatin, and capecitabine. The estimated completion date of this trial was December 2017, and the results are still forthcoming.

Finally, a phase II clinical trial (NCT02015169) was designed to investigate the efficiency and safety of XELOX (capecitabine and oxaliplatin) plus lapatinib treatment in patients with HER2-positive gastric cancer with liver metastasis. The primary outcome was complete resection rate (R0 resection rate). The estimated completion date was May 2017. Despite a small estimated number of participants (32 patients), this trial may determine important issues for other anti-HER2 therapies apart from trastuzumab.

**EGFR Inhibition.** The EGFR transmembrane glycoprotein activates a cascade of tyrosine kinases in Ras/Raf or Akt/mTOR pathways. This receptor was successfully targeted in wild-type KRAS colorectal metastatic cancer with the monoclonal antibodies panitumumab and cetuximab and in squamous cell head and neck cancers with cetuximab. There are also TKIs targeting EGFR, such as erlotinib, which has been approved for lung cancer treatment.

EGFR could be considered an independent prognostic factor of worse outcomes in patients with gastric cancer46; it is overexpressed by 30% to 50% in gastrointestinal tumors and is a potential target in such cases.23

Cetuximab (the EXPAND trial) and panitumumab (the REAL3 trial) failed to demonstrate benefit in advanced gastrointestinal tumors. It is possible that EGFR overexpression is not the leading oncogenic pathway in advanced gastric cancer, but those trials did not select patients by EGFR expression; that approach might be explored in further trials or subgroup analysis.42

More recently, nimotuzumab, another monoclonal anti-EGFR antibody, did not increase OS or progression-free survival in the overall population in a phase II clinical trial for advanced gastric cancer, but those with EGFR overexpression had a substantial benefit, which increased interest in selecting patients by EGFR status for EGFR-targeting therapies.43 Intriguing retrospective biomarker analyses of the COG trial44 suggest that a subpopulation of tumors with EGFR copy number gain may benefit from anti-EGFR therapy, implying that refining the EGFR biomarker may yet yield positive results.

**Immune checkpoint inhibitors.** Upper gastrointestinal (GI) cancers, namely, esophageal cancer, GEJ cancer, and stomach cancer, have high rates of somatic mutations, trailing only melanoma, lung, and bladder cancers with respect to tumor mutational frequency.45 Given the known success of immunotherapy in these highly mutated cancers, basic science and clinical research have been set forth in upper GI cancers, for which the success rate of cytotoxic chemotherapy remains poor.

The purpose of immunotherapy is to shift the balance between proinflammatory immune effector cells and anti-inflammatory suppressive cells. Immune checkpoints refer to many immune system inhibitory pathways that are important for self-tolerance by moderating the duration and amplitude of the physiologic immune response. Tumors use these pathways as mechanisms of tumor resistance through ligand-receptor interactions. Checkpoint inhibitors have the potential to enhance antitumor immunity by altering the ligand receptor relationship between tumor and T cells.46

Currently two classes of immunotherapy are FDA approved, inhibitors of either the PD-1 and its ligand (PD-L1) or CTLA-4.47 PD-L1 is expressed in 35% to 45% of esophageal cancers,48,49 providing a rationale for the use of immunotherapy drugs in these cancers. Recent and ongoing clinical trials have studied the use of PD-1/PD-L1 or CTLA-4 inhibitors as monotherapy or in combination in upper GI cancers.

PD-L1 expression, high MSI, and mismatch repair deficiency can be found in gastric cancer, which may provide a role for immunotherapeutics in treating patients with these diseases. Pembrolizumab, a humanized monoclonal antibody against PD-1, was initially studied in a phase IB trial in advanced pretreated esophageal and GEJ cancers with PD-L1 expression greater than 1%.29 Overall response rate was 30.4% (95% CI, 13.2%–52.9%). A subset analysis of response rate revealed a response rate of 40.0% for adenocarcinoma and 29.4% for squamous cell carcinoma. Later, a phase II trial showed an overall response rate of 13.3% (95% CI, 8.2%–20%) in advanced gastric and GEJ adenocarcinoma, including a complete response rate of 1.4%50 and a partial response rate of 11.9%.51 Patients were required to have PD-L1 expression of at least 1% tumor or stromal cells using immunohistochemistry. This led to FDA accelerated approval for patients with recurrent, locally advanced, or metastatic gastric or GEJ adenocarcinoma. A larger phase III trial that investigated pembrolizumab as second-line treatment for
### TABLE 1. Phase III Clinical Trials in Gastric Cancer With Published Results

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<thead>
<tr>
<th>Trial and Enrollment Period</th>
<th>Source</th>
<th>Setting</th>
<th>Number of Patients</th>
<th>Biomarkers</th>
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<th>Subpopulation Benefit</th>
<th>Conclusion and Observations</th>
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<tr>
<td><strong>AVAGAST</strong>&lt;sup&gt;a&lt;/sup&gt; NCT00548548 (2007–2008)</td>
<td>Ohtsu, 2011&lt;sup&gt;29&lt;/sup&gt;</td>
<td>First-line advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction</td>
<td>774 (1:1)</td>
<td>—</td>
<td>Bevacizumab + cisplatin and capecitabine</td>
<td>Median OS 12.1 vs. 10.1 months (HR 0.87; 95% CI, 0.73–1.03; p = .1002).</td>
<td>Pan-Americans</td>
<td>Did not reach main outcome</td>
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<td>387</td>
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<td>Placebo + cisplatin and capecitabine</td>
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<td><strong>AVATAR</strong> (2009–2010)</td>
<td>Shen and Li, 2015&lt;sup&gt;30&lt;/sup&gt;</td>
<td>First-line Chinese patients with advanced or metastatic gastric or gastroesophageal junction adenocarcinoma</td>
<td>202 (1:1)</td>
<td>—</td>
<td>Bevacizumab + cisplatin and capecitabine</td>
<td>Median OS 10.5 vs. 11.4 months (HR 1.11; 95% CI, 0.79–1.56; p = .5567)</td>
<td>—</td>
<td>Bevacizumab not effective in Chinese population with gastric or gastroesophageal junction adenocarcinoma</td>
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<td>102</td>
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<td>Placebo + cisplatin and capecitabine</td>
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<td><strong>EXPAND</strong> NCT00678535 (2008–2010)</td>
<td>Lordick, 2013&lt;sup&gt;31&lt;/sup&gt;</td>
<td>First-line locally advanced unresectable or metastatic adenocarcinoma of the stomach or gastroesophageal junction</td>
<td>904 (1:1)</td>
<td>—</td>
<td>Cetuximab + capecitabine-cisplatin</td>
<td>Median PFS 4.4 vs. 5.6 months (HR 1.09; 95% CI, 0.92–1.29; p = .32)</td>
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<td>Cetuximab not effective in gastric or gastroesophageal cancer</td>
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<td>Cetuximab-cisplatin alone</td>
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<td><strong>GATSBY</strong> NCT01641939 (2012–2015)</td>
<td>Thuss-Patience, 2017&lt;sup&gt;32&lt;/sup&gt;</td>
<td>HER2-positive advanced gastric cancer that progressed during or after first-line therapy with a combination of at least a platinum agent and a fluoropyrimidine given concurrently</td>
<td>345 (2:1)</td>
<td>HER2</td>
<td>Trastuzumab</td>
<td>Median OS 7.9 vs. 8.6 months (HR 1.15; 95% CI, 0.87–1.51; one-sided p = .86)</td>
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<td>Trastuzumab was not superior to taxane in patients with previously treated, HER2-positive advanced gastric cancer</td>
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<td>228</td>
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<td>Taxane</td>
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<td><strong>GOLD</strong> (2013–2017)</td>
<td>Bang, 2017&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Asian patients with advanced gastric cancer that had progressed after, or during, first-line chemotherapy</td>
<td>525 (1:1)</td>
<td>ATM expression</td>
<td>Olaparib + paclitaxel</td>
<td>Median OS 8.8 vs. 6.9 months (HR 0.77; 97.5% CI, 0.63–1.00; p = .026)</td>
<td>Previous gastrectomy</td>
<td>Olaparib did not demonstrate benefit in Asian patients with refractory advanced gastric cancer</td>
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<td>263</td>
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<td>Placebo + paclitaxel</td>
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<td>Stomach disease</td>
<td>Results also negative in ATM-negative population</td>
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<td><strong>GRANITE-1</strong> NCT00879333 (2009–2010)</td>
<td>Ohtsu, 2013&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Refractory advanced gastric or gastroesophageal adenocarcinoma</td>
<td>650 (2:1)</td>
<td>—</td>
<td>Everolimus + BSC</td>
<td>Median OS 5.4 vs. 4.3 months (HR 0.90; 95% CI, 0.75–1.08; p = .124)</td>
<td>—</td>
<td>Everolimus is not effective in patients with advanced gastric cancer whose disease progressed after one or two lines of previous systemic chemotherapy</td>
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<td>BSC</td>
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<th>Conclusion and Observations</th>
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<tr>
<td>TRIO-013/LOGiC NCT00680901 (2008–2012)</td>
<td>Hecht, 2016⁶⁶</td>
<td>First-line advanced or metastatic adenocarcinoma of the stomach, esophagus, or gastroesophageal junction, with HER2 amplification</td>
<td>545 (1:1)</td>
<td>HER2-positive</td>
<td>Lapatinib + CapeOX</td>
<td>Median OS 12.2 vs. 10.5 months (HR 0.91; 95% CI, 0.73–1.12)</td>
<td>Asian patients (HR 0.68; 95% CI, 0.48–0.96; p = .0261)</td>
<td>Addition of lapatinib to CapeOX did not increase OS in patients with HER2-amplified gastroesophageal adenocarcinoma</td>
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<tr>
<td>RAINBOW NCT01170663 (2010–2012)</td>
<td>Wilke, 2014⁷⁵</td>
<td>Advanced gastric or gastroesophageal junction adenocarcinoma and disease progression after first-line chemotherapy</td>
<td>665 (1:1)</td>
<td>—</td>
<td>Ramucirumab + paclitaxel</td>
<td>Median OS 9.6 vs. 7.4 months (HR 0.807; 95% CI, 0.678–0.962; p = .017)</td>
<td>In second line, ramucirumab with paclitaxel significantly increases OS on advanced gastric or gastroesophageal adenocarcinoma</td>
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<td>Real3 NCT00824785 (2008–2011)</td>
<td>Waddell, 2013⁶⁶</td>
<td>First-line metastatic, or locally advanced esophagogastric adenocarcinoma</td>
<td>553 (1:1)</td>
<td>KRAS</td>
<td>Panitumumab + EOC</td>
<td>Median OS 8.8 vs. 11.3 months (HR 1.37; 95% CI, 1.07–1.76; p = .013)</td>
<td>KRAS mutation (10 patients; HR 0.23; 95% CI, 0.05–1.15)</td>
<td>Addition of panitumumab to EOC chemotherapy, in molecularly unselected population, does not increase OS in first-line metastatic or locally advanced esophagogastric adenocarcinoma</td>
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**Continued**
# TABLE 1. Phase III Clinical Trials in Gastric Cancer With Published Results (Cont’d)

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<tr>
<th>Trial and Enrollment Period</th>
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<th>Setting</th>
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<th>Arms of Treatment</th>
<th>Main Outcome Results</th>
<th>Subpopulation Benefit</th>
<th>Conclusion and Observations</th>
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<tbody>
<tr>
<td>REGARD NCT00917384 (2009–2012)</td>
<td>Fuchs, 2014 [26]</td>
<td>Advanced gastric or gastroesophageal junction adenocarcinoma and disease progression after first-line platinum-containing or fluoropyrimidine-containing chemotherapy</td>
<td>355 (2:1)</td>
<td>Ramucirumab</td>
<td>Median OS 5.2 vs. 3.8 months (HR 0.776; 95% CI, 0.603–0.998; p = .047)</td>
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<td>Ramucirumab monotherapy has survival benefits in patients with advanced gastric or gastroesophageal junction adenocarcinoma progressing after first-line chemotherapy</td>
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<td>238</td>
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<td>Placebo</td>
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<td>RILOMET-1 NCT01697072 (2012–2014)</td>
<td>Catenacci and Cunningham, 2017 [27]</td>
<td>Unresectable locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, with MET positive</td>
<td>609 (1:1)</td>
<td>MET</td>
<td>Median OS 8.8 vs. 10.7 months (HR 1.34; 95% CI, 1.10–1.63; p = .003)</td>
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<td>Negative study</td>
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<td>304</td>
<td>Epirubicin, cisplatin, and capecitabine</td>
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<td>ToGA NCT01041404</td>
<td>Bang et al, 2010 [28]</td>
<td>Gastric or gastro-esophageal junction cancer with overexpression of HER2</td>
<td>594 (1:1)</td>
<td>HER2</td>
<td>Median OS 13.8 vs. 11.1 months (HR 0.74; 95% CI, 0.60–0.91; p = .0046)</td>
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<td>Trastuzumab + chemotherapy increased significantly OS in HER2-positive advanced gastric or gastroesophageal junction cancer</td>
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<td>TyTAN</td>
<td>Satoh, 2014 [29]</td>
<td>Second-line gastric cancer in Asian patients</td>
<td>(1:1)</td>
<td>HER2</td>
<td>Median OS 11.0 vs. 8.9 months (p = .0104)</td>
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<td>Rapamycin + paclitaxel demonstrated statistically significant improvements in OS and PFS in HER2-positive IHC3+ tumors and in Chinese patients</td>
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<td>132</td>
<td>Paclitaxel</td>
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*In a further biomarker evaluation of the AVAGAST trial, high plasma VEGF-A (HR 0.72; 95% CI, 0.57–0.93) and low tumor neuropilin-1 (HR 0.75; 95% CI, 0.59–0.97) were found to be strong biomarker candidates for predicting clinical outcomes in patients with advanced gastric cancer treated with bevacizumab. [30] |

Abbreviations: ATM, ataxia telangiectasia–mutated protein; BSC, best supportive care; CapeOX, capecitabine and oxaliplatin; EOC, epirubicin, oxaliplatin, and capecitabine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Date of source: January 10, 2018.
patients with advanced gastric or GEJ adenocarcinoma did not meet its primary endpoint of OS (HR 0.82; 95% CI, 0.66–1.03; p = .042) in patients whose tumors expressed PD-L1 greater than 1%.52 It is possible that PD-L1 is not a good biomarker in gastric cancer or that limiting its expression to 1% was too optimistic. It is possible that selecting patients with higher PD-L1 expression would provide superior outcomes.

Nivolumab is a human monoclonal IgG4 antibody that inhibits PD-1 expressed on activated T cells. A phase II trial included patients with advanced pretreated esophageal cancer, not preselected by PD-L1 status, and demonstrated a 17% objective response rate (95% CI, 10%–28%).50,53 A similar response rate of 11% was reported in a phase III trial that included advanced gastric or GEJ tumors intolerant to at least two previous lines of chemotherapy. There was also an improvement in 12-month OS rate with nivolumab of 26.2% (95% CI, 20.7%–32.0%) compared with 10.9% (95% CI, 6.2%–17.0%) with placebo.54 A head-to-head phase III trial comparing nivolumab with chemotherapy including docetaxel or paclitaxel in a similar cohort of chemorefractory patients is ongoing.55

Tremelimumab inhibits CTLA-4, a protein receptor member of the immunoglobulin superfamily that functions as an immune checkpoint, that when expressed on the surface of T helper cells, transmits an inhibitory signal to T cells when bound to CD80 or CD86 on the surface of antigen-presenting cells.56 A phase II trial for patients with pretreated metastatic gastric and esophageal adenocarcinomas showed no objective response rates when treated with tremelimumab. Despite this, duration of response in a small select group of patient was encouraging.57

There are limited data to show that combination immunotherapy is more effective than monotherapy. A phase I/II study combining ipilimumab and nivolumab led to durable responses and long-term OS in heavily pretreated patients with advanced gastric, esophageal, and GEJ cancer.58 There are ongoing studies of combination therapy with mogamulizumab, a humanized monoclonal antibody targeting chemokine receptor, and nivolumab in advanced upper GI cancers.59,60 Additional ongoing studies in patients with metastatic upper GI cancers include the combination of LAG525, which targets LAG-3, and spartalizumab, an anti–PD-1 combination.61 Furthermore, tremelimumab and durvalumab, a human immunoglobulin G1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD-1 and CD-80, are also being studied.62

Historically, chemotherapy and radiation therapy have been used in different stages of upper GI cancers. In metastatic upper GI cancers, chemotherapy provides response rates of 35% to 40%, with median survival benefit of 9 to 11 months. Radiation therapy has been used in locally advanced disease as well as palliatively in patients with metastatic disease. With modest benefit seen in the treatment of metastatic disease with chemotherapy, the most logical step was to study immunotherapeutics. Despite some preclinical promise, the clinical benefit of in upper GI cancers has been modest and has not been proved to be superior to chemotherapy. Knowing that chemotherapy has proven benefit, trials have now begun to look at combining chemotherapy with immunotherapy and/or radiation therapy.

The scientific rationale for the use of chemotherapy combined with immunotherapy is based on preclinical data suggesting that cytotoxic agents may act as immunomodulatory agents through tumor antigen presentation. This leads to an upregulation of the expression of tumor antigens and major histocompatibility complex class I molecules, to which the antigens bind. Through an alternative pathway, chemotherapy may also upregulate costimulatory molecules such as B7-1 or downregulate coinhibitory molecules such as PD-L1 or B7-H4 expressed on the tumor cell surface. In doing so, this enhances the strength of effector T-cell activity, preferential depletes regulatory T cells, and liberates homeostatic or inflammatory cytokines.63-66 Chemotherapy may also render tumor cells more sensitive to T cell–mediated lysis through fas-, perforin-, and granzyme B–dependent mechanisms.67,68

Using this understanding, clinical trials have begun studying the use of combination chemotherapy with immunotherapy in upper GI cancers. A phase III clinical trial is currently evaluating the use of nivolumab and ipilimumab, nivolumab combined with fluorouracil and cisplatin, or fluorouracil and cisplatin alone.69,70 Primary endpoints of this study include progression-free survival and OS in previously untreated patients with advanced unresectable, recurrent, or metastatic esophageal squamous cell carcinoma. There are ongoing trials of pembrolizumab alone or in combination with chemotherapy versus chemotherapy alone in first-line gastric or GEJ adenocarcinoma as well as in the neoadjuvant and adjuvant setting.71 Another phase I/II study will evaluate the safety of durvalumab in combination with oxaliplatin/capcitabine in the metastatic setting.

RT is a key modality in treating many esophageal cancers. Like chemotherapy, radiation has been found in preclinical models to have immunomodulatory effects through different mechanisms, including the creation of neoantigens, increased expression of proinflammatory cytokines capable of activating leukocytes, as well as upregulation and recruitment of immune cells into the tumor microenvironment.72,73 PD-L1 has been reported to be upregulated in the tumor microenvironment after ionizing radiation in mice.74 This increased PD-L1 expression suppresses the antitumor properties of effector T cells, providing a rational combination of immunotherapy and RT.

Using preclinical models,63,75,76 combination RT and immunotherapy has received limited study. Previous small retrospective series have shown acceptable tolerability and some enhanced response rates with combined immunotherapy and RT in different disease subtypes.77,78 On the basis of these data, clinical trials are ongoing in upper GI cancers. Pembrolizumab combined with RT is being studied in metastatic esophageal79 as well as in advanced cancers of the stomach and GEJ.80 In the neoadjuvant setting, pembrolizumab, durvalumab, nivolumab, and ipilimumab are being studied in addition to chemoradiation.81-83
Finally, the discovery of tumor-associated antigens provides specific targets for new immunotherapies, including using these tumor-associated antigens in cell-based therapies by developing autologous T cells that specifically target these antigens in patients whose tumors express them. Two common tumor-associated antigens that are known to be expressed in esophageal cancers are melanoma-associated antigen 3 and NY-ESO-1. In 2017, Lu et al.84 addressed 17 patients with metastatic cancer who were treated with a major histocompatibility complex class II–restricted T-cell receptor targeting the cancer germline antigen melanoma-associated antigen 3. Patients received a schedule based on a lymphodepleting preparative regimen, followed by adoptive transfer of purified CD4+ T cells retrovirally transduced with melanoma-associated antigen 3 TCR plus a systemic high dose of interleukin-2. Among nine patients who were treated at the highest dose level, objective partial responses were observed in a patient with esophageal cancer (duration at the highest dose level, objective partial responses were observed in a patient with esophageal cancer (duration 4 months).84 Ongoing trials will hopefully shed light on the observed in a patient with esophageal cancer (duration 4 months).84 Ongoing trials will hopefully shed light on the

**PIK3CA.** The complex PI3K/Akt/mTOR pathway has an important role in different cellular mechanisms, such as cell growth, cell proliferation, protein translation, and metabolism. Dysregulation of this pathway, which involves many different tyrosine kinases, is frequently observed in many tumors and has led to the development of many targeted therapies in this pathway that have been tested in different solid tumors, including gastric cancer.85 In a TCGA report, 80% of EBV tumors and 42% of MSI tumors have PIK3CA mutations, suggesting that this pathway is a possible target for new treatments in gastric cancer.

The GRANITE phase III clinical trial, testing everolimus for previously treated advanced gastric cancer, failed to improve survival; however, PIK3CA mutations were not tested, and thus, patients were not selected or assessed for PIK3CA.84 Targeting the PI3KCA pathway in only mutated patients might be a promising biomarker for future assessment in patients with gastric cancer. Some AKT inhibitors, such as atrasertib and AZD5363, are also being tested in gastric cancer, and the results are forthcoming.5

**Angiogenesis.** The high relevance of new blood vessels for cancer growth and survival is well known.86 VEGF, a protein with different isoforms, is a stimulator of endothelial cell growth that is highly expressed in different solid tumors, particularly in necrotic or hypoxic areas. Overexpression of angiogenic markers is associated with more aggressive disease; thus, these markers are potential targets in gastric cancer therapy.

Bevacizumab is an anti-VEGF antibody widely used in different solid tumors, such as colorectal, ovarian, breast, and lung cancer,85,87 but it still did not demonstrate a clinical benefit in gastric cancer. The AVATAR and AVAGAST phase III clinical trials failed to demonstrate the clinical benefit of bevacizumab in advanced gastric or GEJ cancer.29,30 However, ramucirumab, a fully human monoclonal antibody potent against VEGFR-2, demonstrated benefit in the second-line treatment of advanced gastric cancer following the REGARD26 and RAINBOW25 phase III clinical trials. In the REGARD trial, ramucirumab monotherapy versus best supportive care significantly increased OS in second-line treatment of advanced gastric or GEJ adenocarcinomas. The median OS was 5.2 months (interquartile range, 2.3–9.9 months) in patients in the ramucirumab and 3.8 months (interquartile range, 1.7–7.1 months) in those in the placebo group (HR 0.776; 95% CI, 0.603–0.998).25 In the RAINBOW trial, ramucirumab with paclitaxel increased progression-free survival and OS compared with placebo plus paclitaxel. OS was significantly longer in the ramucirumab plus paclitaxel group than in the placebo plus paclitaxel group (median, 9.6 months [95% CI, 8.5–10.8 months] vs. 7.4 months [95% CI, 6.3–8.4 months]; HR 0.807; 95% CI, 0.678–0.962).25

The TKI apatinib inhibits VEGFR-2 and demonstrated efficacy and safety in phase II and III clinical trials in patients with chemotherapy-refractory advanced or metastatic gastric cancer, becoming a possible treatment in third- or further-line therapies.88 Despite previous positive results in trials, there are some concerns regarding the clinical benefit of ramucirumab and apatinib in gastric cancer. There is a marginal benefit of apatinib (1.8 months) and ramucirumab (1.4–2.2 months), but hopefully, further research on biomarkers, combination therapies, sequencing, or maintenance therapies might bring more substantial results for targeting VEGF in gastric cancer.89,90

**PARP.** PARPs are a group of enzymes that catalyze the transfer of ADP-ribose to different intracellular proteins.91 PARPs are relevant in many cellular processes, such as transcription, replication, recombination, and DNA repair.92 Their role in DNA repair is particularly relevant because certain tumors defective in homologous recombination mechanisms may rely on PARP-mediated DNA repair for survival and are sensitive to its inhibition.93 PARP inhibition already has an important role in BRCA-associated breast and ovarian cancers and might have additional importance in other cancers, such as gastric adenocarcinoma.94 Higher PARP-1 expression can be found in gastric cancer, and that might be related to more advanced disease and worse prognosis.

After some promising results in a phase II clinical trial, in the GOLD phase III clinical trial, the PARP inhibitor olaparib did not significantly increase OS in patients with advanced gastric cancer, including an ataxia telangiectasia–mutated protein–negative population.33 In some trials, statistical methods (such as a statistically significant p value < .025) and the lack of BRCA biomarker stratification could be some of the reasons for unmet outcomes. Other trials to address PARP inhibitors in gastric cancer are still ongoing. A phase I clinical trial (NCT01123876) is testing velaparib, a PARP inhibitor, with FOLFIRI in gastric cancer. A phase I/II trial (NCT03008278) is still recruiting subjects to test the effectiveness of olaparib and ramucirumab (an anti-VEGFR-2 antibody) in treating patients with metastatic or locally recurrent gastric cancer or GEJ cancer that cannot be removed by surgery. Novel combinations and possible biomarker tai-
loring are challenging issues that might result in changes in clinical practices in the near future.

FGFR. Fibroblast growth factors are a family of proteins that interact with four tyrosine kinase transmembrane receptors (FGFRs).95 FGFRs are downstream of different intracellular signaling pathways, including RAS-MAPK, PI3K-AKT, and STAT, and thus regulate different cellular processes, such as proliferation, survival, migration, differentiation, and metabolism.36,95 Interference in this pathway, such as gene amplification, chromosomal translocation, or mutations, is associated with tumor initiation, survival, proliferation, and invasion, particularly in diffuse-type cancers such as gastric cancer.96

To date, there are 11 trials registered at ClinicalTrials.gov targeting FGFR in gastric cancer. In the phase II SHINE trial, AZD4547, an FGFR2 TKI, compared with paclitaxel in patients with gastric cancer with FGFR2 amplification/polysomy failed to improve the main outcome of progression-free survival.97

Some drugs, such as dovitinib, foretinib, and pazopanib are multi-TKIs, in which inhibition includes FGFR.95 A phase II trial (NCT01719549) is testing the multi-TKI dovitinib in gastric cancer with FGFR2 amplification/amplification. Another phase II trial (NCT01921673) is evaluating the role of dovitinib plus docetaxel as second-line chemotherapy in patients with metastatic or unresectable gastric cancer. Both trials are completed, but the results have not yet been published. It is not yet known if targeting only one FGFR will have positive results in gastric cancer, but there might be a place for multi-TKIs that inhibit FGFR along with other kinase pathways.

CONCLUSION AND FUTURE PERSPECTIVES

Currently, the treatment of advanced EGC is still a challenge for oncologists and patients worldwide. EGC is different from other types of tumors, such as lung, prostate, and melanoma, because it lacks extensive, innovative, and effective options based on driver mutations and immunotherapy. Only HER2 expression is validated as a predictive biomarker, which could help tailor patient treatment. To date, only trastuzumab and ramucirumab are well established for the treatment of advanced EGC. More recently, nivolumab showed a modest benefit in later lines of advanced EGC in the ATTRACTION-2 study.54 Novel molecular classifications such as proposed by TCGA and the ACRG will benefit the identification of potential biomarkers that might help the development of new target therapies, the design of new clinical trials, and retrospective subanalysis of completed trials. In HER2 amplification tumors, VEGF, PARP, EGFR, PIK3CA, and FGFR are promising pathways that could be sources of novel target drugs in the near future. However, more extensive translational and clinical studies are warranted to optimize these approaches.

ACKNOWLEDGMENT

All authors contributed equally to this manuscript.

References


Global Epidemiology, Prevention, and Management of Hepatocellular Carcinoma

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OVERVIEW

The incidence rate of hepatocellular carcinoma (HCC) is rising. It is one of the most common cancers worldwide and accounts for substantial morbidity and mortality. Chronic hepatitis B virus (HBV) infection, chronic hepatitis C virus (HCV) infection, and nonalcoholic fatty liver disease (NAFLD) are the most important etiologies of HCC, and effective screening and management strategies are crucial to reduce the HCC risk. For HBV, which accounts for the majority of HCC cases, most infections were acquired via perinatal and early horizontal transmission. Universal vaccination of newborns has led to a decline in HCC incidence compared with the pre-vaccination era. Effective antiviral therapies with nucleos(t)ide analogues or pegylated interferon reduced the incidence of HCC. For HCV, the emergence of effective direct-acting antiviral (DAA) agents has substantially improved cure rates; therefore all patients with HCV should be considered for DAA treatment. The most important obstacle in eliminating HCV is access to therapy. For NAFLD, the global incidence is increasing rapidly, thus its impact on HCC incidence may be explosive. Progression to HCC in NAFLD happens particularly in those with nonalcoholic steatohepatitis (NASH) and exacerbated by metabolic syndrome, or PNPLA3 gene polymorphism. Lifestyle changes are imperative while drug therapy has yet to demonstrate substantive protective effects on HCC prevention. For management of HCC, early diagnosis via imaging surveillance among persons with HCC risk factors remains the most important strategy to identify early-stage disease appropriate for resection or transplantation.

HCC incidence rates have been rising in the past 3 decades, and these trends are expected to remain through 2030. According to the World Health Organization (WHO), HCC is the fifth most common cancer worldwide and the second most common cause of cancer-related death in 2015. Several important risk factors have been identified, including chronic HBV infection, chronic HCV infection, NAFLD and NASH, alcoholic liver disease, hereditary hemochromatosis, and any other causes leading to cirrhosis. Although effective antiviral therapies are available to treat chronic HBV and HCV, virally mediated HCC remains the etiology for the majority of HCC cases globally. Moreover, the NAFLD/NASH pandemic, especially in developed countries, will hinder the decline of HCC incidence, if not increase it. In this article, these three important risk factors (i.e., HBV, HCV, and NAFLD/NASH) will be discussed regarding their impacts on the global epidemiology, prevention, and management of HCC.

HEPATITIS B VIRUS

Global Epidemiology of HBV

WHO estimated that 257 million persons, corresponding to 3.5% of the global population, are chronically infected with HBV as of the year 2015. Large regional variation of chronic HBV has been observed: the most endemic areas are the Western Pacific (6.2% of the residing population) and African (6.1%) regions followed by the East Mediterranean (3.3%), Southeast Asia (2.0%), and European (1.6%) regions and the region of the Americas (0.7%). The establishment of HBV chronicity depends on the age of exposure. The risk is greater than 90% for infants and children younger than age 2 compared with 0% to 2% for adults. Therefore, most chronic HBV infections were acquired vertically (i.e., mother to child transmission). Universal birth-dose HBV vaccination reduces the prevalence of chronic HBV in newborns; thus, most patients with chronic HBV were born in the prevaccination era.
Patients with chronic HBV are at risk for liver-related complications, namely cirrhosis and HCC. The incidence of these complications parallels the prevalence of chronic HBV, and therefore, the global distributions of chronic HBV and HCC mirror each other. It is estimated that chronic HBV is etiologically implicated in as many as 50% to 80% of all HCC cases, especially in HBV endemic areas (where chronic HBV prevalence is greater than 8%). The lifetime risk of chronic HBV carriers to develop cirrhosis and/or HCC is 15% to 40%. The relative risk ratio of HCC in patients with chronic HBV ranged from 14 to 223 compared with that in noncarriers. The risk is substantially increased in those with cirrhosis. According to a systematic review in Asia, the incidence rates of HCC were 0.2, 0.6, and 3.7 per 100 person-years in inactive carriers, noncirrhotic chronic HBV, and cirrhotic chronic HBV, respectively.

In 2015, nearly 1 million persons died because of complications of chronic HBV. In contrast to the reductions in mortality from other important infections, such as HIV, tuberculosis, and malaria, the mortality from chronic HBV–related complications increased over the past decade. Specifically, HBV cirrhosis–related deaths were 241,700 in 1990 compared with 312,400 in 2010. The numbers of deaths from chronic HBV–related HCC were 210,200 in 1990 compared with 341,400 in 2010. Deaths from HBV-associated HCC occur at a younger age in sub-Saharan Africa (median age 38.9) than in the Western Pacific region (median age 54.5).

Prevention and Management of HBV Infection

Primary prevention: Active and passive immunization. Preventing HBV infection is the primary step in prevention of HCC. Because the vast majority of chronic HBV infection is acquired vertically from infected mothers, newborn vaccination confers active immunization and plays an essential role in primary prevention of chronic HBV–related HCC. WHO recommends HBV vaccination of all newborns, with the first dose given within 24 hours of birth (timely birth dose). The birth dose should be followed by two or three subsequent doses within the first 6 months of infancy. In some countries, passive immunization with hepatitis B immune globulin given with the birth dose vaccine is also recommended. This combination scheme is more effective than either HBV vaccine or hepatitis B immune globulin alone. Before universal newborn immunization, the vertical transmission rates in newborns of hepatitis B e antigen (HBeAg)–positive mothers were 70% to 100% in Asia and 40% in Africa, whereas in newborns of HBeAg-negative mothers, the rates were 5% to 30% in Asia and 5% in Africa. In contrast, when newborn immunization was implemented, the vertical transmission rates in newborns of HBeAg-positive mothers and HBeAg-negative mothers were 20% and 0%, respectively.

Failure of vaccine protection primarily occurs in newborns of highly viremic mothers who are usually HBeAg positive with high serum HBV DNA more than $10^{6}$ copies per milliliter. Treating these mothers with an effective antiviral (e.g., tenofovir disoproxil fumarate) on top of newborn immunization effectively reduces the risk of vertical transmission as recommended by major international guidelines.

Since the worldwide introduction of HBV vaccine from the 1980s to the early 2000s, the proportion of children younger than age 5 with chronic HBV fell from 4.7% in the prevaccination era to 1.3% in 2015, although a relatively high rate of 3.0% is still seen in young children in the African region. HBV immunization in newborns has been shown to reduce the incidence of HCC. In a study from Thailand, the age-standardized incidence rate of HCC in nonvaccinated children older than age 10 was 0.88 per million compared with 0.07 per million in vaccinated children. Similar findings were reported in a Taiwanese study, where the age- and gender-adjusted relative risk of HCC was 0.31 for the vaccinated cohort compared with the nonvaccinated cohort of children age 6 to 19. Development of HCC despite vaccination was associated with incomplete HBV vaccination (odds ratio [OR], 29.5) and absence of hepatitis B immune globulin administration in those born from HBeAg-positive mothers (OR, 9.43).

Secondary prevention: Risk factors modification. In patients who are already chronic HBV carriers, the risk of HCC development is higher in those with certain host factors or viral factors. Host factors include older age, male gender, African origin, the presence of cirrhosis, chronic hepatic necroinflammation, alcohol use, coinfection with chronic HCV or HIV, metabolic syndrome, and genetic polymorphism. Viral factors include high HBV DNA levels and presence of specific viral mutations, such as core promoter mutation or pre-S deletion. Although many of these host and viral factors are nonmodifiable, HBV DNA level can now be substantially reduced by antiviral drugs; hence, it is now the main treatment target for chronic HBV.

There are two main classes of drugs for control of viral replication: interferon (IFN) and nucleos(t)ide analogs (NAs). The use of NA is shown to reduce the risk of HCC in patients with chronic HBV. Despite the fact that lamivudine is no longer recommended as first-line NA in chronic HBV, multiple well-designed studies in the past have shown the beneficial effect of lamivudine in HCC reduction. Emerging data suggest the coherent protective effect of the more potent first-line NAs: entecavir and tenofovir disoproxil.
fumarate. For instance, entecavir-treated patients were less likely to develop HCC than matched controls (hazard ratio, 0.37). Although these comparative studies were mainly performed in Asian patients, data are limited for white patients. A recent European cohort showed that the annual HCC incidence rate decreased from 1.22% within the first 5 years to 0.73% after the first 5 years of entecavir or tenofovir disoproxil fumarate. Other studies involving non-Asian patients were not direct comparative studies, which compare the annual HCC incidence rates between NA-treated patients with a theoretical predicted risk calculated by validated risk scores for the development of HCC. NA s are shown to be associated with fibrosis regression and, to a lesser extent, reversal of cirrhosis, which is another contributing factor to the protection against HCC development.

Although data are more heterogeneous and less well-established compared with those in chronic HBV, the use of IFN in chronic HBV was also shown to reduce the risk of HCC in a selected subgroup of patients with early cirrhosis who responded to IFN compared with controls. Nevertheless, IFN response rate in chronic HBV is disappointing (20%–30%) and incurs numerous adverse effects. It is only considered as an initial treatment for patients with mild to moderate chronic HBV without advanced cirrhosis. Other modifiable host factors should be optimized if feasible. These include limitation of alcohol intake, screening for and treatment of coinfection chronic HBV and HIV, and control of metabolic risk factors, such as insulin resistance, and concurrent fatty liver disease.

Tertiary prevention: Continuation of antiviral in established HCC. The general approach to HCC is covered later in this article. Specific to chronic HBV, in those who already developed HCC, tertiary prevention mainly involves initiation (if not given before the HCC) or continuation of antiviral therapy. The beneficial effect of NA is observed in patients who received curative therapies for HCC. In those who underwent curative liver resection for HCC, the 6-year HCC recurrence rate in NA-treated patients was significantly lower than that in untreated patients (45.6% vs. 54.6%, p < .001). Also, in patients receiving radiofrequency ablation, NA treatment has been shown to be associated with reduced risk of HCC recurrence (2-year recurrence rate: 41.8% vs. 54.3%, p < .05). Although NA is highly effective at preventing HBV reactivation and graft hepatitis after liver transplantation, there is yet not any evidence showing the beneficial effect of NA in prevention of HCC recurrence. The effect of NA on HCC for patients with inoperable HCC undergoing loco-regional therapy is also not well defined. These patients should still be maintained on NA to prevent hepatic flares because of unsuppressed virologic replication.

HEPATITIS C VIRUS
Global Epidemiology of HCV

Globally, 71 million persons are living with HCV infection. In 2015, there were 1.75 million new HCV infections. The areas of highest incidence are the Eastern Mediterranean Region (62.5 per 100,000) and the European Region (61.8 per 100,000), where the predominant route of transmission is unsafe health care injections and illicit injection drug use, respectively. In the United States, approximately 3.5 million individuals are chronically infected with HCV, with over 75% of these in the “baby boomer” age cohort; most were infected before the discovery of HCV and the subsequent development of modern screening techniques for blood products. More recently, injection drug use is the most common mode of acquisition of HCV infection in younger populations. Chronic infection with HCV leading to fibrosis, cirrhosis, and associated molecular and genomic alterations is a major contributing factor to liver cancer in the United States, and it is associated with 50% of cases. The chronic infection rate after acute infection with HCV is 75% to 85%, with 60% to 70% developing chronic liver disease, which leads to cirrhosis in 5% to 20% and 1% to 5% dying from liver failure or cancer. Most of this decades-long progression is absent symptoms, possibly contributing to complacency on the part of the public and health professionals. However, this prolonged period also allows a window of opportunity for prevention by treating indolent HCV infections before the onset of liver cancer. The oncology community would benefit from increased awareness of the rising burden of hepatitis-related cancers and should consider opportunities to prevent and manage the identified risk factors for rapidly growing HCC in their patient populations.

Individuals born between 1945 and 1965 (“baby boomers”) represent the cohort with the highest rates of chronic HCV infection and, concomitantly, the highest rates of liver cancer–related mortality. The most common cancer types associated with HCV infection are primary liver cancers, HCC, and intrahepatic cholangiocarcinoma. Additionally, associations have been reported with hematologic malignancies in particular B-cell non-Hodgkin lymphoma (NHL). Marginal zone lymphoma, lymphoplasmacytic lymphoma, Burkitt lymphoma, and follicular lymphoma have also been reported. Evidence on associations of HCV with multiple extrahepatic solid tumors is suggestive but inconclusive.

Deaths related to HCV, including liver cancer, have increased substantially and now exceed deaths caused by 60 other reportable infections combined, including HIV, pneumococcal disease, and tuberculosis. This is in spite of calls for screening the baby boomer cohort as well as other at-risk individuals with a one-time HCV antibody test. Effective treatment of those with chronic HCV infection is available and seems to be associated with improved outcomes in patients with cancer; however, it is underutilized. Barriers related to awareness and cost are being addressed, but it is important for oncologists to assure that their at-risk patients are tested and treated when indicated. In addition to patients managed for active treatment, many in the cancer survivor population may be at risk, and HCV-related liver cancers represent a potentially avoidable cause of second primary cancers.

Prevention of HCV Infection: Identification of Persons With HCV Infection

Current guidelines for screening in the general population include recommendations for individuals in the baby
boomer birth cohort and those at risk of acquisition of HCV through individual behaviors (Table 1). There are no existing recommendations specific to HCV screening in the cancer population.

**Evolving rationale for screening in the general population.** The recommendations for HCV screening in the general population have evolved over time from risk-based testing to currently include everyone born between the years 1945 and 1965. In 1998, the Centers for Disease Control and Prevention (CDC) issued its first recommendations for HCV testing in individuals with risk factors for HCV infection. The principal risk factor for chronic HCV infection is a history of intravenous drug use, even one time. Additional risk factors include receiving a blood transfusion or solid organ transplantation before the year 1992 and clotting factors before 1987, people on chronic hemodialysis, evidence of chronic liver disease as evidenced by an elevated alanine aminotransferase, individuals who are HIV positive, health care workers with occupational exposure (needle stick), and children born of HCV-positive mothers.

**TABLE 1. The Centers for Disease Control and Prevention Testing Recommendations for HCV Infection**

<table>
<thead>
<tr>
<th>Population</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults born from 1945 to 1965 should be tested once (without prior ascertainment of HCV risk factors)</td>
<td>Adults born from 1945 to 1965 should be tested once (without prior ascertainment of HCV risk factors)</td>
</tr>
<tr>
<td>Individuals who:</td>
<td>Individuals who:</td>
</tr>
<tr>
<td>• Are current users for injection drugs</td>
<td>• Are current users for injection drugs</td>
</tr>
<tr>
<td>• Have ever injected drugs, including those who have done so one or a few times many years ago</td>
<td>• Have ever injected drugs, including those who have done so one or a few times many years ago</td>
</tr>
<tr>
<td>• Have certain medical conditions including:</td>
<td>• Have certain medical conditions including:</td>
</tr>
<tr>
<td>– Persons who received clotting factor concentrates produced before 1987</td>
<td>– Persons who received clotting factor concentrates produced before 1987</td>
</tr>
<tr>
<td>– Persons who were ever on long-term hemodialysis</td>
<td>– Persons who were ever on long-term hemodialysis</td>
</tr>
<tr>
<td>– Persons with persistently abnormal alanine aminotransferase levels</td>
<td>– Persons with persistently abnormal alanine aminotransferase levels</td>
</tr>
<tr>
<td>– Individuals who are infected with HIV</td>
<td>– Individuals who are infected with HIV</td>
</tr>
<tr>
<td>• Were prior recipients of transfusions or organ transplants, including those who</td>
<td>• Were prior recipients of transfusions or organ transplants, including those who</td>
</tr>
<tr>
<td>– Were notified they had received blood from a donor who later tested positive for HCV infection</td>
<td>– Were notified they had received blood from a donor who later tested positive for HCV infection</td>
</tr>
<tr>
<td>– Received a transfusion of blood, a transfusion of blood components, or an organ transplant before July 1992</td>
<td>– Received a transfusion of blood, a transfusion of blood components, or an organ transplant before July 1992</td>
</tr>
<tr>
<td>Persons who might have been exposed to HCV within the past 6 months (test for RNA or follow-up testing for HCV antibody)</td>
<td>Persons who might have been exposed to HCV within the past 6 months (test for RNA or follow-up testing for HCV antibody)</td>
</tr>
<tr>
<td>Individuals for whom HCV testing is recommended based on a recognized exposure</td>
<td>• Health care, emergency medical, and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood</td>
</tr>
<tr>
<td>• Children born to women who are HCV-positive</td>
<td>• Children born to women who are HCV-positive</td>
</tr>
<tr>
<td>Individuals for whom the need for HCV testing is uncertain</td>
<td>• Persons who have been the recipient of transplanted tissue (including but not limited to musculoskeletal, skin, sperm, and ova)</td>
</tr>
<tr>
<td>• Individuals who have used noninjection illegal drugs, including intranasal cocaine</td>
<td>• Individuals who have used noninjection illegal drugs, including intranasal cocaine</td>
</tr>
<tr>
<td>• Individuals with a history of tattooing or body piercing</td>
<td>• Individuals with a history of tattooing or body piercing</td>
</tr>
<tr>
<td>• Individuals with a history of multiple sex partners or sexually transmitted diseases</td>
<td>• Individuals with a history of multiple sex partners or sexually transmitted diseases</td>
</tr>
<tr>
<td>• Persons who have been long-term sex partners with individuals who are HCV-infected</td>
<td>• Persons who have been long-term sex partners with individuals who are HCV-infected</td>
</tr>
<tr>
<td>Individuals for whom HCV testing is not recommended</td>
<td>Unless they have risk factors for infection as detailed above, routine screening is not recommended for:</td>
</tr>
<tr>
<td>• Individuals employed as health care workers, including emergency medical and public safety workers</td>
<td>• Individuals employed as health care workers, including emergency medical and public safety workers</td>
</tr>
<tr>
<td>• Women who are pregnant</td>
<td>• Women who are pregnant</td>
</tr>
<tr>
<td>• Nonsexual partners/relatives/household contacts of individuals who are HCV-infected</td>
<td>• Nonsexual partners/relatives/household contacts of individuals who are HCV-infected</td>
</tr>
</tbody>
</table>

Abbreviation: HCV, hepatitis C virus.
However, risk-based HCV screening is inadequate for many reasons, and better screening methods are needed. Principally, many people with chronic HCV infection do not report or recall a specific identifiable risk factor, and thus, infected patients could be missed. Even among people with access to health care and an elevated alanine aminotransferase, the HCV screening rate is low. Thus, the CDC in 2012 and the U.S. Preventive Services Task Force in 2013 updated their recommendations to include one-time HCV screening for all people born between 1945 and 1965. The rationale for birth cohort screening is the disproportionate prevalence of HCV infection in this population. According to data from the National Health and Nutrition Examination Survey in 2003 and 2010, people born between 1945 and 1965 accounted for over 80% of chronic HCV infection in the United States, with an estimated prevalence of 2.6% or six times that of the general population. Along with the CDC and the U.S. Preventive Services Task Force, the American Association for the Study of Liver Disease (AASLD), the Infectious Diseases Society of America, the European Association for the Study of Liver Disease, and WHO have recommended birth cohort screening in addition to screening based on risk factors. Screening is recommended one time for individuals without ongoing HCV risk behavior. In individuals with ongoing risk (e.g., active intravenous drug users), no specific interval of testing is recommended.

**HCV screening tests.** The initial test to screen for HCV infection is serum testing for anti-HCV antibodies or the anti-HCV test. Anti-HCV antibodies typically form from 2 to 6 months after initial HCV infection. If the anti-HCV test is reactive, this indicates HCV exposure in the past but does not differentiate current infection (chronic or acute) from past infection that is now resolved from either spontaneous viral clearance or after anti-HCV therapy. Thus, HCV RNA is the confirmatory test performed in all patients with a positive anti-HCV test to diagnose current infection. In addition, HCV RNA viral load obtained before the initiation of anti-HCV therapy can be used to guide duration of anti-HCV therapy. HCV RNA testing could be considered in immunocompromised patients who might not be able to mount a reactive anti-HCV test result. Interpretation of anti-HCV and HCV RNA tests is detailed in Table 2.

**Limitations to HCV testing.** Persons with recent HCV exposure in the past 6 months may have a false-negative test result, because it takes up to 6 months for the antibodies to form. In such cases, the HCV RNA test serves as a confirmatory test. Immunosuppressed individuals may not generate anti-HCV antibodies. In such cases, HCV RNA testing would confirm current infection. A biologic false-positive anti-HCV test can occur in 20% of patients, in whom the anti-HCV test is positive but if an HCV RNA is done, it would be negative. These patients do not have active HCV infection. Consider testing with another anti-HCV screening assay. Up to 20% of individuals may spontaneously resolve an HCV infection after exposure. Such individuals will have positive anti-HCV antibody testing but negative HCV RNA testing. Patients successfully treated for HCV will retain anti-HCV antibodies but have a negative HCV polymerase chain reaction.

**What does HCV RNA mean?** Patients with positive anti-HCV test and detectable HCV RNA have current HCV infection and are well served by referral to an HCV specialist who can evaluate and initiated DAA therapy if not contraindicated. HCV specialists will also order an HCV genotype test, a diagnostic test in which results will guide selection of DAA treatment. HCV genotyping is not a screening test for HCV infection. Patients with current HCV infection also need counseling about modifying other risk factors for liver fibrosis, including alcohol moderation, optimal weight maintenance, and management of metabolic syndrome and steatosis. If a patient has an anti-HCV–positive result but the HCV RNA is negative, then this patient does not have current HCV infection. No additional workup or monitoring is necessary, unless the patient has a new risk factor for HCV infection, in which case additional HCV RNA testing can be followed to assess for a new infection. If the patient received anti-HCV treatment and achieved sustained viral response in the setting of advance fibrosis or cirrhosis, then this patient needs lifelong surveillance for HCC.

**Management of HCV Infection**

**Anti-HCV therapy.** The introduction of all oral, highly effective, well-tolerated DAA therapy has revolutionized the management of chronic HCV. In the span of only a few years since the introduction of the first DAA agent, almost everyone with chronic HCV infection can be cured with a minimum of side effects. Accordingly, the AASLD/Infectious Diseases Society of America joint guidelines on the management of chronic HCV infection recommend that everyone with chronic HCV infection be referred to an HCV treatment provider for consideration of antiviral therapy. The only exception to this recommendation is for those with a short life expectancy who would not be impacted by eradication of HCV.

Antiviral therapy against HCV has a positive impact on the risk of development of HCV-associated cancers. For instance, the use of IFN-containing regimens was associated

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**TABLE 2. Interpretation of Anti-HCV and HCV RNA Tests**

<table>
<thead>
<tr>
<th>Anti-HCV</th>
<th>HCV RNA PCR</th>
<th>Interpretation(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Active HCV infection</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Previous exposure with spontaneous clearance, previous HCV treatment with SVR, or false-positive antibody</td>
</tr>
<tr>
<td>Negative</td>
<td>Positive</td>
<td>Immunosuppressed patient or recent infection (less than 6 months)</td>
</tr>
<tr>
<td>Negative</td>
<td>Negative</td>
<td>No previous exposure to HCV</td>
</tr>
</tbody>
</table>

Abbreviations: HCV, hepatitis C virus; PCR, polymerase chain reaction; SVR, sustained virologic response.
with a more than 70% reduction in the risk of developing primary HCC\textsuperscript{72,83} and reduced the risk of primary NHL development to 0% among patients with resolved HCV infection (vs. 2.56% among patients with persistent infection).\textsuperscript{84} The new IFN-free regimens with DAAs have shown excellent rates (greater than 90%–95%) of sustained virologic response (SVR), which is regarded as virologic cure.\textsuperscript{77} DAA-induced SVR is associated with a 71% to 76% reduction in HCC risk compared with treatment failure.\textsuperscript{85,86} Currently available DAA therapy is presented in Fig. 1.

A few recent studies have raised concerns on the increase risk of HCC occurrence or recurrence after DAA therapy.\textsuperscript{87-89} However, several studies support that treatment with DAAs is not associated with increased HCC risk compared with treatment with IFN or in DAA-unexposed patients.\textsuperscript{85,86,90-92}

Although well-designed prospective studies are conducted to clarify this controversy, surveillance for HCC occurrence or recurrence is required among patients with an SVR at risk for liver disease progression, irrespective of the antiviral regimen used.\textsuperscript{67}

**DAA therapy to reduce risk of cirrhosis, HCC, and NHL development.** Professional societies have published guidelines for diagnosis, management, and treatment of HCV infection in patients without cancer\textsuperscript{77,78} and patients with hematologic malignancies or hematopoietic cell transplant recipients,\textsuperscript{93,94} but these guidelines do not include recommendations for all patients with cancer.

HCV guidelines in patients without cancer recommend that all patients with HCV be treated, except those with a short life expectancy who cannot be remediated by HCV therapy, liver transplantation, or another directed therapy to prevent complications of this curable infection, including HCC.\textsuperscript{77} The HCC risk in HCV-infected patients increases radically after they develop cirrhosis, but a lower HCC risk is still present in patients with advanced fibrosis.\textsuperscript{85} SVR after IFN-based regimens is associated with improvement in liver fibrosis and necrosis in liver biopsies in 39% to 73% of patients, with reversal of cirrhosis observed in 49% of the cases.\textsuperscript{95} In the same way, improvement of liver stiffness has been reported in patients with HCV-associated advanced liver disease and DAA-induced SVR.\textsuperscript{96} Treatment of HCV infection may also reduce the risk or prevent extrahepatic complications, including mixed cryoglobulinemia, porphyria cutanea tarda, diabetes mellitus, cardiovascular disease, and B-cell NHL.\textsuperscript{97-99}

Recent data highlight the potential consequences of delaying antiviral treatment on subsequent risk of HCC and support treatment of all patients with HCV before their progression to advanced fibrosis and cirrhosis, because progression to cirrhosis might be associated with substantial downstream costs related to the need for lifelong HCC surveillance and/or cancer care for those who develop HCC.\textsuperscript{96} Likewise, deferral treatment practices based on fibrosis stage alone are also inadequate in HCV-associated NHL, because advanced liver disease has been reported in only 18% of the patients at the time of NHL diagnosis.\textsuperscript{98}

**NASH**

**Introduction**

NAFLD, the hepatic manifestation of metabolic syndrome, exhibits a histologic spectrum ranging from simple steatosis to NASH, a more aggressive form of damage with inflammation and necrosis.\textsuperscript{100} NASH can lead to fibrosis and finally, cirrhosis with its complications, including HCC. Cirrhosis is the main risk factor to develop HCC, and it is present in 70% to 90% of HCC cases.\textsuperscript{101} The most common causes of cirrhosis are usually HBV, HCV, and alcoholic liver disease, but with the sharp growth in the prevalence of obesity and diabetes mellitus, NASH is at the moment the most common etiology for chronic liver disease worldwide.\textsuperscript{102} However, recent evidence has shown that a substantial proportion of patients with NAFLD or NASH progress to HCC in the absence of cirrhosis, implicating obesity and diabetes mellitus as independent risk factors for HCC.\textsuperscript{103} Unfortunately, the mechanisms by which NASH promotes the development of HCC are only beginning to be studied, which is why its natural history and prognosis are still controversial.

**Global Epidemiology of NASH**

The rising incidence of NAFLD and NASH has led to an alarming rise of NASH-related HCC as well as an increasing indication for HCC-related liver transplantation in the United States.\textsuperscript{104} On average, the global prevalence of NAFLD is about 24%, with the highest rates reported in South America (31%) and the Middle East (32%), followed by Asia (27%), the United States (24%), and Europe (23%), whereas Africa has the lowest rate (14%).\textsuperscript{105} In addition, it has been estimated that up to 25% of patients with NAFLD can progress
to NASH and that up to 20% of patients with NASH have cirrhosis.106

Risk Factors for NASH-Related HCC

NASH. A systematic review by White et al107 showed that NASH-associated cirrhosis carried a 2.4% to 12.8% increased risk of HCC. Several studies have reported cases of NASH without cirrhosis. In this regard, Kawada et al108 studied 1,168 patients who underwent hepatic resection for HCC, observing that six of eight patients with NASH-related HCC did not have cirrhosis. Likewise, Paradis et al109 reported that a number of patients with NASH developed HCC in the absence of fibrosis compared with HCC in the setting of other underlying liver disease. However, it is important to mention that several studies have reported HCC in the setting of noncirrhotic NAFLD. These patients, mainly older men, have less aggressive tumors, and they are less likely to be diagnosed by surveillance because of current guidelines that recommend HCC screening only in patients with cirrhosis.110-112 One proposed hypothesis to explain the development of HCC in patients with noncirrhotic NAFLD is that, in the presence of metabolic syndrome, hepatocellular adenoma may incur a malignant transformation.113,114

Obesity. Obesity predisposes to HCC development by lipid accumulation inside hepatocytes, which in turn, leads to chronic low-grade inflammation.115 Obesity affects more than one-third of the U.S. population, being present in between 37% and 66% of patients with NAFLD and representing 36.6% of HCC causes in the United States and 16% in Europe.115-117 The risk of developing steatohepatitis is higher in obese individuals than nonobese individuals,118 and obesity increases the relative risk of dying of cancer (Fig. 2).119 Obese individuals have an increased risk (1.5- to 4.0-fold) of HCC; in addition, men with HCC and a body mass index (BMI) of greater than 35 kg/m² have a higher increase in mortality. Some studies have reported that a BMI higher than 25 kg/m² is a risk factor for hepatocarcinogenesis.120 A systematic review revealed that persons who were overweight (BMI 25.0–29.9 kg/m²) or obese (BMI more than 30.0 kg/m²) had 17% and 89% increased HCC risk compared with those of normal weight, respectively (Table 3).121

Diabetes mellitus. Type 2 diabetes mellitus is a component of metabolic syndrome, and it is strongly related to obesity. It is estimated that one in 10 middle-aged American adults has diabetes mellitus. The association between HCC and diabetes mellitus has been reported in many studies. People with diabetes have a 2.31-fold increased risk of developing HCC and a 2.43-fold increased risk of HCC mortality compared with individuals without diabetes.134 In a large prospective study by El-Serag et al,135 patients with diabetes were shown to have a significantly higher incidence of NAFLD and HCC than persons without diabetes (NAFLD/HCC incidence rate: 18.13/2.39 vs. 9.55/0.87 per 10,000 person-years, respectively; p < .0001). Additionally, diabetes mellitus is an independent risk factor for developing HCC, with an OR of 2.87 (95% CI, 2.49–3.30).136

The comparison for each relative risk was between men in the highest BMI category and men in the reference category (BMI 18.5–24.9). Liver cancer had the highest relative risk. Results of the linear test for trend were significant for all cancer sites (p < .05).

Abbreviation: BMI, body mass index.

Adapted from Calle et al.119
### TABLE 3. Systematic Review of the Association Between Obesity and HCC: Epidemiologic Evidence

<table>
<thead>
<tr>
<th>First Author, Year, Country</th>
<th>Study Type and Total Population Sample Size (N)</th>
<th>BMI (kg/m²)</th>
<th>Obese Population</th>
<th>HCC Risk (95% CI)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>White men ICD OD</td>
<td>1.44 (1.28–1.61)</td>
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<td></td>
<td></td>
<td>Black men ICD OD</td>
<td>0.68 (0.49–0.94)</td>
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<tr>
<td>Calle et al, 2003, United States</td>
<td>Cohort N: 900,053</td>
<td>18.5–24.9</td>
<td>RR: 1.0</td>
<td>Women</td>
<td></td>
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<td></td>
<td></td>
<td>25–29.9</td>
<td>1.13 (0.94–1.34)</td>
<td>1.02 (0.80–1.31)</td>
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<td></td>
<td></td>
<td>30–34.9</td>
<td>1.90 (1.46–2.47)</td>
<td>1.40 (0.97–2.00)</td>
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<td></td>
<td></td>
<td>35–39.9</td>
<td>4.52 (2.94–6.94)</td>
<td>1.68 (0.93–3.05)</td>
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<tr>
<td>Chen et al, 2008, Taiwan</td>
<td>Cohort N: 23,820</td>
<td>HBV and HCV negative</td>
<td>RR: 1.0</td>
<td>Women</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>&lt; 23</td>
<td>0.88 (0.41–1.86)</td>
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<td></td>
<td></td>
<td>23–24.9</td>
<td>0.86 (0.42–1.74)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>2.36 (0.91–6.17)</td>
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<td></td>
<td></td>
<td>HBV positive only</td>
<td>RR: 1.0</td>
<td>Women</td>
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<td></td>
<td></td>
<td>&lt; 23</td>
<td>1.40 (0.97–2.02)</td>
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<td></td>
<td></td>
<td>23–24.9</td>
<td>1.17 (0.81–1.69)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>1.36 (0.64–2.89)</td>
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<td></td>
<td></td>
<td>HCV positive only</td>
<td>RR: 1.0</td>
<td>Women</td>
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<td></td>
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<td>&lt; 23</td>
<td>1.05 (0.41–2.73)</td>
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<td></td>
<td></td>
<td>23–24.9</td>
<td>3.02 (1.48–6.14)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>4.13 (1.38–12.4)</td>
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<td>Jee et al, 2008, Korea</td>
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<td>23–24.9</td>
<td>HR: 1.0</td>
<td>Women</td>
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<td></td>
<td></td>
<td>25–29.9</td>
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<td>1.14 (0.97–1.35)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>1.63 (1.27–2.10)</td>
<td>1.39 (1.00–1.94)</td>
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<td>Kuriyama et al, 2005, Japan</td>
<td>Cohort N: 25,539</td>
<td>18.5–24.9</td>
<td>RR: 1.0</td>
<td>Women</td>
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<td></td>
<td></td>
<td>25–27.4</td>
<td>0.80 (0.40–1.63)</td>
<td>1.30 (0.54–3.16)</td>
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<td>27.5–29.9</td>
<td>1.14 (0.46–2.87)</td>
<td>0.91 (0.30–2.80)</td>
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<td>Samanic et al, 2006, Sweden</td>
<td>Cohort N: 362,552</td>
<td>18.5–24.9</td>
<td>RR: 1.0</td>
<td>Women</td>
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<td></td>
<td></td>
<td>25–29.9</td>
<td>1.45 (1.06–1.98)</td>
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<tr>
<td></td>
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<td>≥ 30</td>
<td>3.13 (2.04–4.79)</td>
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<tr>
<td>Batty et al, 2005, United Kingdom</td>
<td>Cohort N: 17,102</td>
<td>18.5–24.9</td>
<td>HR: 1.0</td>
<td>Women</td>
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<tr>
<td></td>
<td></td>
<td>25–29.9</td>
<td>0.91 (0.50–1.65)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>3.55 (1.46–8.63)</td>
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<tr>
<td>Rapp et al, 2005, Austria</td>
<td>Cohort N: 67,447</td>
<td>18.5–24.9</td>
<td>HR: 1.0</td>
<td>Women</td>
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<tr>
<td></td>
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<td>25–29.9</td>
<td>1.32 (0.73–2.37)</td>
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<td></td>
<td></td>
<td>≥ 30</td>
<td>1.67 (0.75–3.72)</td>
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<td>Wolk et al, 2001, Sweden</td>
<td>Cohort N: 28,129</td>
<td>Swedish population</td>
<td>SIR: 1.0</td>
<td>Women</td>
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<td></td>
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<td>ICD OD</td>
<td>2.4 (1.6–3.4)</td>
<td>3.60 (2.0–6.0)</td>
<td>1.7 (0.9–2.9)</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Metabolic syndrome. Metabolic syndrome is a group of metabolic disorders composed of hyperglycemia, abdominal obesity, high blood pressure, hypertriglyceridemia, and low high-density lipoprotein. Metabolic syndrome occurs when the patient has three of these metabolic conditions. Currently, up to 25% of the U.S. population is affected by metabolic syndrome. Epidemiologic studies have estimated that the risk of HCC is increased by 1.5- to 2.0-fold in individuals with metabolic syndrome. A systematic review by Jinjuvadia et al showed that patients with metabolic syndrome have a 81% increase risk of HCC (relative risk, 1.81; 95% CI, 1.37–2.41). This could be related to specific molecular pathways of liver tumorigenesis, such as the oxidative stress and reactive oxygen species production, high levels of insulin growth factor-1, or the dysregulation of inflammatory cytokines.

Patatin-like phospholipase-3 gene. The patatin-like phospholipase-3 gene is localized on human chromosome 22, and its protein is expressed in the liver and adipose tissue. It has shown a strong activity in lipolysis and triglyceride hydrolysis in adipocytes. In 2015, Xu et al performed a meta-analysis to assess a relationship between the patatin-like phospholipase-3 rs738409 polymorphism and susceptibility to NAFLD, including NASH. The analysis, which included 23 case-control studies of 6,071 patients with NAFLD and 10,366 controls, showed a significant association between the rs738409 polymorphism and NAFLD risk in all genetic models (OR, 3.41; 95% CI, 2.57–4.52; p < .00001) as well as with NASH risk (OR, 4.44; 95% CI, 3.39–5.82; p < .00001). Interestingly, this genetic variation has been frequently observed in the Hispanic population with NAFLD. Additionally, Singal et al reported in their systematic review with meta-analysis an increased HCC risk in patients with cirrhosis (OR, 1.40; 95% CI, 1.12–1.75). This risk was higher in patients with NASH or alcohol-related cirrhosis (OR, 1.67; 95% CI, 1.27–2.21) than in those with other etiologies of cirrhosis (OR, 1.33; 95% CI, 0.96–1.82). Therefore, it is evident that patatin-like phospholipase-3 is a crucial risk factor for hepatic steatosis, severe fibrosis progression, and HCC development.

Management of NASH
It is important to recognize that all potential therapies for NASH studied in clinical trials have had inconsistent results, and thus, definitive treatment is not currently available. However, diet and weight loss have led to the best outcomes for the patient with this disorder. A 7% to 10% weight loss
is the target of most lifestyle interventions, and it results in improvement of liver enzymes and histology. Pioglitazone and vitamin E have been essential in the NASH therapy, and they have shown improvement of liver histology \(^{147}\) in patients with and without diabetes mellitus with biopsy-proven NASH. \(^{148,149}\) The pharmacotherapy for NASH has focused on modulation of metabolic pathways, inflammatory cascades, and/or mechanisms impacting fibrosis, and numerous agents are currently being investigated in phase II and III clinical trials. In randomized trials, drugs to inhibit the progression of NASH to cirrhosis found that obeticholic acid, \(^{150}\) selonsertib, \(^{151}\) and elafibranor \(^{152}\) can cause a decrease in hepatic fat and fibrosis. Elafibranor was developed as a peroxisome proliferator–activated receptor-α/δ agonist, and its effects have been shown in reduction of steatosis, fibrosis, and inflammation in patients with NAFLD. \(^{153}\) Interestingly, Ratziu et al. \(^{153}\) showed that using the highest dose (120 mg) of elafibranor could resolve NASH without aggravating the grade of fibrosis (when considering “aggravating” as any NAFLD stage that implicates fibrosis). Furthermore, they showed that elafibranor improved the cardiometabolic risk in patients with NASH.

**Prevention of NASH-Related HCC**

Cirrhosis remains the primary indication for implementing HCC surveillance; therefore, the AASLD guidelines recommend that patients with NAFLD or cirrhosis should be screened for HCC every 6 months. \(^{154}\) In general, surveillance is performed by ultrasonography, but vigilance in the NAFLD population is a challenge, because screening with abdominal ultrasound in obese patients can be inaccurate. Currently, there is a lack of recommendations for surveillance of patients with NASH and without cirrhosis, probably because of the difficulty of identifying patients with NASH without a liver biopsy. However, recent blood-based biomarkers could be an affordable alternative for identification of patients at high risk of NASH and advanced fibrosis. \(^{155}\)

Recent evidence suggests possible strategies to prevent HCC development in patients with NAFLD/NASH. \(^{156}\) These strategies concentrate on lifestyle changes to reduce progression of liver damage and use metabolically active drugs, such as metformin and statins. In patients with type 2 diabetes mellitus and metabolic syndrome, studies have shown that regular aerobic exercise and weight loss reduce insulin resistance and can improve inflammatory activity as well as diabetes mellitus compensation. \(^{156,157}\) In this regard, in a phosphatase and tensin homolog–deficient mouse model, which is characterized by spontaneous development of both NAFLD and HCC, the incidence of HCC was lower in exercised animals (71%) than in sedentary animals [100%; \(p < .05\)]. \(^{158}\) Regular exercise has shown the inhibition of mTOR and the activation of
HCC Management

HCC heterogeneity complicates the clarification of the mechanisms of cancer development and the development and implementation of effective treatments. Only 10% to 13% of patients with HCC can be cured with liver transplant, surgical resection, or tumor ablation therapies. Nowadays, the Barcelona Clinic Liver Cancer classification is the most widely accepted staging system; it is the only one that considers the liver function, the stage of tumor, and the physical status of patients with HCC. Additionally, it is the most used classification for clinical trials of new drugs to treat HCC and in clinical practice. The early diagnosis of HCC and intervention are essential so that patients with HCC can meet the criteria for curative resection or liver transplantation at the time of diagnosis.

Diagnosis of HCC. The diagnostic tests include biopsy and noninvasive tests, such as ultrasound, quadruple-phase multidetector CT (unenhanced, arterial, venous, and delayed phases), and dynamic contrast-enhanced MRI. The use of alpha-fetoprotein is no longer recommended, because it is insufficiently sensitive and specific for surveillance or diagnostic testing.

Ultrasound is key for an early HCC diagnosis, because it can detect tumors less than 1 cm in size. According to AASLD guidelines, these tumors should be monitored with ultrasonography at intervals of 3 to 6 months. Contrast-enhanced ultrasonography should not be used as a diagnostic tool because of its lack of specificity for HCC. Tumors greater than 1 cm found by ultrasonography screening should be evaluated with two of three dynamic studies: contrast ultrasonography, CT scan, or MRI with contrast. When the lesion has atypical imaging features, the tumor should be biopsied or undergo fine-needle aspiration.

The definitive diagnosis of HCC is made by biopsy or a dynamic technique, which shows an arterial hyperenhancement with venous/delayed-phase washout of contrast. Unfortunately, biopsies have an up to 30% false-negative rate, which is why an expert pathologist should evaluate the biopsies, especially for smaller lesions. Pathologists can fine-tune the HCC diagnosis by using the current markers CD34, HSP-70, CK7, glypican 3, and glutamine synthetase. A negative biopsy for HCC should be followed by imaging at 3 to 6 months until the lesion shows characteristic changes for HCC or the lesion enlarges or disappears.

Treatment of HCC. Patients should be stratified by disease stage in the clinical setting. For each stage, there should be an indicated treatment. Unfortunately, there is practically no treatment for late-phase HCC that improves survival, confirming why patients with cirrhosis should be screened for HCC every 6 months. Patients with HCC require a multidisciplinary evaluation for an optimal outcome, and their care team should comprise hepatologists, radiologists, pathologists, oncologists, internists, interventional radiologists, transplant surgeons, hepatobiliary surgeons, and nurses. Currently, the strategy to treat HCC is the Barcelona Clinic Liver Cancer scheme (Fig. 4).

There are several HCC treatment options, such as surgical resection, liver transplantation, percutaneous ablation, and noncurative treatments (sorafenib, transarterial chemoembolization). In general, surgical resection or liver transplantation is the first option to treat early-stage HCC; however, resection should be offered for patients who have an optimal profile. Liver transplantation should follow Milan criteria: a single tumor of 5 cm or up to three nodules of 3 cm. Local ablation should be offered when a patient is not a candidate for surgical resection or as a bridge to liver transplantation. Radiofrequency ablation and percutaneous ethanol injection are effective for small tumors, but radiofrequency ablation is superior for tumors larger than 2 cm than percutaneous ethanol injection. Transarterial chemoembolization is recommended for patients who do not have vascular invasion or extrahepatic spread and are not candidates for liver transplantation, surgical resection, or local ablation because of large tumor size or multifocal tumor. Radioembolization with 90Y-labeled glass beads has been shown to induce tumor necrosis and better survival rates compared with transarterial chemoembolization. Moreover, it has shown effectiveness to treat patients with intermediate-stage disease with multiple or large tumors that do not respond to transarterial chemoembolization, as well as patients with advanced-stage disease with single-tumor...
and lobar portal vein tumor thrombosis. However, radioembolization with $^{90}$Y-labeled glass beads should not be recommended as standard therapy, because current data are all based on retrospective or noncontrolled prospective studies. Finally, sorafenib is recommended for patients with advanced-stage disease and those who have exhausted other therapeutic options. This drug has shown a relevant improvement in survival and the delay of tumor progression. Nevertheless, palliative treatment should be offered for patients with disseminated HCC.

CONCLUSION

HCC is a common cause of death and malignancy worldwide. HCC etiologies vary depending on geographic area, lifestyle, and advanced medical care, but currently, most HCC cases are related to chronic infection from HBV or HCV. NAFLD/NASH and excessive alcohol consumption are other important risk factors for the development of HCC. With the rising rates of obesity and diabetes mellitus as well as the declining levels of alcohol consumption and viral hepatitis infection in many areas, NAFLD/NASH will become the most important risk factor for HCC. Consequently, it should be emphasized on surveillance and early diagnosis of HCC in at-risk populations. For HBV and HCV, universal prevention measures, education on high-risk behaviors, and screening programs for blood donors are crucial to prevent and reduce HCC cases. However, vaccination is the key to prevent HBV-related HCC. Current antiviral therapies for HBV and HCV infection can only decrease HCC and cannot entirely eradicate it. Treatment of HCC has improved substantially over the last decades, with several curative options. Novel therapies, such as radioembolization with $^{90}$Y-labeled glass beads, and medications, such as sorafenib and regorafenib, have shown improvements in survival rates, but research still must be continued. Additional studies are needed to improve prevention strategies and advance management of patients with HCC, especially in the field of tumor regression therapies.

ACKNOWLEDGMENT

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References


free therapy.


Is There a Precise Adjuvant Therapy for Esophagogastric Carcinoma?

Elizabeth Cartwright, MBBS, Florence K. Keane, MD, Peter C. Enzinger, MD, Theodore Hong, MD, and Ian Chau, MD

OVERVIEW

Esophagogastric cancer remains a leading cause of cancer-related mortality worldwide. The prognosis for patients with locally advanced disease is poor and the majority of patients with operable tumors treated with surgery alone will have recurrent disease. A multimodal approach to treatment with adjunctive chemotherapy or chemoradiotherapy is therefore the standard of care for these patients. However, there is no global consensus on the optimal treatment strategy and international guidelines vary. National clinical trials inform local practice: neoadjuvant, perioperative, and adjuvant chemotherapy and radiotherapy combinations are all possible treatment options in the management of resectable esophagogastric cancer. A number of clinical trials are ongoing, which seek to directly compare multimodal treatment options and hope to provide clarity in this area. Furthermore, increased understanding of the molecular and genetic features of esophagogastric cancer may help to guide management of operable disease by determining optimal patient selection through identification of predictive biomarkers of response and the application of novel targeted agents.

Long-term survival following surgical resection of esophagogastric cancer is poor, with 5-year survival of less than 50% following surgery alone for patients with stage II or higher disease.1,2 Adjunctive therapies improve survival for these patients, although standard practice varies globally. The European Society of Medical Oncology guidelines recommend a perioperative chemotherapy approach for patients with stage IB resectable gastric cancer or higher and for patients who have not received neoadjuvant chemotherapy, postoperative chemoradiotherapy (CRT), or chemotherapy.3 For patients with locally advanced esophagogastric junction (EGJ) adenocarcinoma, either perioperative chemotherapy or neoadjuvant CRT is recommended.4 For patients with stage T1b gastric cancer, the current U.S. National Comprehensive Cancer Network guidelines recommend upfront surgery followed by surveillance or adjuvant chemotherapy or CRT, depending on pathologic stage; for patients with stage T1b or higher disease, perioperative chemotherapy or alternatively CRT is recommended.5 For patients with locally advanced EGJ adenocarcinoma, neoadjuvant CRT prior to surgery is recommended.6 In Asia, where clinical practice has been shaped by high disease incidence, national screening programs, and an early stage of diagnosis, adjuvant chemotherapy following surgery for resectable gastric cancer remains the standard of care.7

PERIOPERATIVE CHEMOTHERAPY

In Europe, a perioperative approach has widely been adopted for patients with locally advanced EGJ and gastric cancer on the basis of two large phase III randomized controlled trials. The U.K. Medical Research Council (MRC) MAGIC trial showed significant improvement in 5-year overall survival (OS; 23%–36%; p = .009) with perioperative epirubicin, cisplatin, and infusional 5-fluorouracil (5-FU; ECF; three cycles of ECF pre- and postoperatively) for 503 patients with stage II or higher operable esophagogastric adenocarcinoma versus surgery alone.8 A similar improvement in OS was reported in the French FNCLCC/FFCD trial for 224 patients with operable esophagogastric adenocarcinoma treated with perioperative cisplatin and 5-FU (CF; two to three cycles of CF preoperatively and three to four cycles postoperatively) for 503 patients with stage II or higher operable esophagogastric adenocarcinoma versus surgery alone.9 In both trials, perioperative chemotherapy was associated with increased R0 resection rates and earlier pathologic tumor (T) and nodal (N) stage at surgery compared with surgery alone.8,9 In the MRC MAGIC and FNCLCC/FFCD trials, gastric and lower esophageal adenocarcinoma, respectively, were the predominant anatomic subtypes by similar proportions and together these studies provide evidence for a perioperative approach in both resectable EGJ and gastric adenocarcinomas. A subsequent meta-analysis including the MAGIC and FNCLCC/FFCD trials among 14 randomized controlled trials investigating perioperative

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chemo(radio)therapy versus surgery in esophagogastric cancer reported that perioperative chemotherapy is associated with increased R0 resection rates, a more favorable tumor stage at surgery, increased disease-free survival (DFS), and a significantly longer OS (hazard ratio [HR], 0.81; 95% CI, 0.73–0.89), with an absolute increase in survival of 9% at 5 years.10

More recently, the German AIO group presented the practice-changing results of the FLOT4 study. After the observed efficacy of dose intensification with docetaxel in the advanced setting, FLOT4 sought to compare perioperative docetaxel-based triplet chemotherapy, four cycles pre- and postoperatively of 5-FU, leucovorin, oxaliplatin, and docetaxel (FLOT) every 2 weeks to three cycles of pre- and postoperative epirubicin, cisplatin, and capecitabine (ECX)/ECF 3 times weekly for patients with gastric and EGJ adenocarcinoma. Following encouraging phase II results demonstrating a significant increase in pathologic complete regression (pCR) with perioperative FLOT compared with perioperative ECX/F, the phase III clinical trial of 716 patients (56% of patients with EGJ tumors) showed that perioperative FLOT was associated with a significant improvement in median progression-free survival from 18 to 30 months (HR 0.75; CI, 0.62–0.91; p = .0004) and improved median OS from 35 to 50 months (HR 0.77; CI, 0.63–0.94; p = .012) with a projected improvement in 5-year OS from 36% to 45%.11,12

Perioperative FLOT chemotherapy was associated with an increased proportion of patients undergoing resection surgery and increased R0 resection rates compared with the ECX/F arm (p = .011). Surgical morbidity and mortality were not increased in the FLOT arm and although more grade 3 to 4 occurrences of infection, diarrhea, neutropenia, and sensory disturbance were reported with FLOT, the overall tolerability was comparable with ECX/F. The ECX/F arm in FLOT4 performed as expected, with a near identical projected 3-year OS rate to that reported in the perioperative ECX chemotherapy arm in the contemporaneously published STO3 trial, indicating that the improvement in OS seen was not as a result of an underperforming control arm.13 In the subgroup analyses, in the subgroup analyses, the benefit of perioperative FLOT was observed across all tumor subgroups, including signet cell tumors, Siewert type 1 esophageal tumors (HR 0.60), node negative tumors (HR 0.64), and small tumors (HR 0.66).14

Despite the improvement in OS with perioperative chemotherapy demonstrated in large phase III trials, a significant proportion of patients will not tolerate the postoperative component of this treatment. In the MRC MAGIC trial, 42% of patients in the chemotherapy arm completed all six cycles of chemotherapy.8 Similar results were reported in FLOT4, where although 91% of patients in the ECF/ECX chemotherapy arm completed preoperative chemotherapy, only 52% of patients started postoperative chemotherapy and 37% completed the protocol. This decrease in uptake was mirrored in the FLOT chemotherapy arm. However, it is noted that patients treated with FLOT were more likely to commence postoperative chemotherapy (60%), and those who did were more likely to complete postoperative chemotherapy (46%) than those in the ECX/F arm.12 In clinical practice, for patients who are unable to tolerate the postoperative component of perioperative chemotherapy, the results in the neoadjuvant setting suggest that this omission might be acceptable, especially if there has been excessive toxicity with preoperative therapy or prolonged postoperative recovery.

**PREOPERATIVE CHEMOTHERAPY**

Long-term results of the MRC OE02 trial among patients with esophageal adenocarcinoma and squamous cell carcinoma reported significant improvement in 5-year OS from 17.1% to 23% (HR 0.84; 95% CI, 0.72–0.98; p = .03) with neoadjuvant CF (two cycles) compared with surgery alone.15 However, results in this setting have been inconsistent, with the European EORTC 40954 and RTOG 8911 trials showing no significant improvement in OS with neoadjuvant chemotherapy.16 Subsequent meta-analyses have reported a 2-year absolute survival benefit of 7%, with most benefit seen among patients with junctional tumors and among patients with adenocarcinoma.17,18 The U.K. MRC OE05 study, a phase III randomized controlled trial of 897 patients with resectable esophageal and EGJ Siewert type 1 and 2 adenocarcinoma, showed that increasing the duration and intensity of preoperative chemotherapy with four cycles of ECX versus two cycles of CF did not improve median OS (23.4 vs. 26.1 months; p = .19).19 Four cycles of neoadjuvant ECX cannot therefore be considered standard of care; however, patients with Siewert type 3 and gastric adenocarcinoma were not included in this study.

There have been few trials directly comparing neoadjuvant and adjuvant chemotherapy. However, in 2016, the SAKK 43/99 trial published the updated results of a prospective randomized phase III trial comparing four cycles of

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**PRACTICAL APPLICATIONS**

- Perioperative chemotherapy or neoadjuvant chemo(radio)therapy is standard of care in resectable esophagogastric cancer.
- Patients who are suitable for triplet chemotherapy in the perioperative setting should be considered for chemotherapy with 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel.
- Adjuvant chemotherapy with or without radiotherapy is an alternative approach for patients with resectable gastric and esophagogastric junction cancer who have not received preoperative treatment.
- The use of targeted therapies in operable esophagogastric cancer is limited to clinical trials and their role remains investigational.
- Putative prognostic and predictive biomarkers are under investigation in operable esophagogastric cancer, with metabolic response, pathologic regression, and microsatellite instability showing promise in tailoring therapy.
neoadjuvant docetaxel, cisplatin, and 5-FU and four cycles of postoperative docetaxel, cisplatin, and 5-FU for patients with locally advanced resectable gastric cancer. The trial closed early because of slow accrual after 69 patients were enrolled and therefore was not powered sufficiently for survival, which may explain the lack of any observed differences in event-free survival and OS at 10 years. The group concluded that preoperative docetaxel, cisplatin, and 5-FU may be delivered with higher dose intensity and better feasibility than postoperative docetaxel, cisplatin, and 5-FU with the anticipated benefits in terms of efficacy at surgical resection in the preoperative treatment arm, with 60% of patients (19 of 32) achieving tumor downstaging.

**ADJUVANT CHEMOTHERAPY**

In Asia, where patients tend to present with earlier-stage disease, adjuvant chemotherapy remains a standard of care. The ACTS-GC and CLASSIC trials have both reported a significant improvement in OS with adjuvant chemotherapy following D2 gastrectomy in Asian populations. The ACTS-GC trial compared postoperative S1 (the combination of an oral prodrug of 5-FU, tegafur, and oxonic acid) at 40 mg/m² for 28 days followed by a 2-week break for 1 year versus surgery following a minimum D2 dissection for patients with stage II or higher gastric adenocarcinoma. The trial was stopped early following an interim analysis at 1 year after 1,059 patients were recruited, showing an improvement in OS in the S1 group compared with surgery alone (p = .002). The updated 5-year survival showed a maintained benefit with a significant improvement in 5-year OS from 61% to 72% with adjuvant S1 across patients in all disease stages. However, the utility of S1 for non-Asian populations has not been established and S1 remains an investigational drug in the United States and Europe. The phase III CLASSIC trial was conducted in centers across South Korea, China, and Taiwan and included patients with stage II or higher gastric adenocarcinoma following D2 dissection. The investigators compared 520 patients who received 6 months of capecitabine and oxaliplatin with 515 patients who were treated with surgery alone. The results showed an improvement in DFS at 3 years from 59% in the surgery-alone group to 74% in the chemotherapy arm (HR 0.56; 95% CI, 0.44–0.72; p < .0001), with an improved 5-year OS in the adjuvant chemotherapy arm at 78% versus 69% (HR 0.66; 95% CI, 0.51–0.85; p = .0015).

Several trials have investigated the role of sequential chemotherapy in the adjuvant setting. In Europe, the ITACA study showed that sequential irinotecan and 5-FU followed by docetaxel compared with 5-FU alone among 1,100 patients with resectable adenocarcinoma of the stomach and EGJ was not associated with a significant difference in DFS (HR 1.0; 95% CI, 0.85–1.17; p = .97) or OS (HR 0.98; 95% CI, 0.82–1.18; p = .87). The Japanese SAMIT trial of 1495 patients with T4a/b, NO-2 gastric adenocarcinoma following D2 gastrectomy showed no improvement in DFS with sequential treatment with paclitaxel and S1 or tegafur/uracil (HR 0.92; 95% CI, 0.80–1.07; p = .273). Early-phase clinical trials have shown feasibility of dose intensification with docetaxel in addition to S1 in the adjuvant setting and encouraging 3-year OS data for 62 patients with stage III gastric cancer treated with S1 plus docetaxel after D2 gastrectomy.

**ADJUNCTIVE CHEMORADIOThERAPY**

In resectable gastric and EGJ cancer, treatment paradigms incorporating CRT and chemotherapy have developed in parallel, reflecting the two competing risks of recurrence in patients with locally advanced disease—locoregional recurrence and distant metastasis. Randomized data support the role of CRT in the adjuvant setting for patients with high-risk (T3/T4, node-positive, poorly cohesive-type) tumors, but delivery of treatment is challenging in the postoperative setting, raising interest in the role of neoadjuvant CRT. For patients with resected, margin-negative stage IB to IV (M0) gastric or EGJ cancer, adjuvant CRT is recommended based on the results of the Intergroup 0116 trial. In resectable gastric and EGJ cancer, treatment paradigms incorporating CRT and chemotherapy have developed in parallel, reflecting the two competing risks of recurrence in patients with locally advanced disease—locoregional recurrence and distant metastasis. Randomized data support the role of CRT in the adjuvant setting for patients with high-risk (T3/T4, node-positive, poorly cohesive-type) tumors, but delivery of treatment is challenging in the postoperative setting, raising interest in the role of neoadjuvant CRT.
Given the challenges associated with delivery of adjuvant CRT, many favor perioperative chemotherapy as described in the MAGIC trial. Although only approximately 40% of patients enrolled were able to complete all recommended therapy, 85% of patients received all three cycles of preoperative chemotherapy and all patients received at least one cycle of chemotherapy. By combining multigent chemotherapy with CRT the CALGB 80101 trial set out to improve OS by harnessing both the improvement in locoregional control seen in Intergroup 0116 and the reduction in distant metastases seen in the MAGIC trial. A total of 546 patients with margin-negative gastric or EGJ adenocarcinoma were randomly assigned to postoperative 5-FU and leucovorin before and after CRT versus postoperative ECF before and after CRT. However, there was no significant difference in 5-year OS or DFS between the two arms, with 5-year OS of 44% in both arms (HR 0.98; 95% CI, 0.78–1.24; p = .69).

Similarly to the previously discussed trials of adjuvant therapy, many patients were unable to complete a full course of adjuvant treatment, with approximately 66% of patients completing a full course of chemotherapy and CRT as planned.

Assessment of the role of postoperative CRT is particularly important for patients who have undergone a margin-negative resection with D2 lymph node dissection, as most patients enrolled in Intergroup 0116 had a D0 or D1 lymph node dissection. The ARTIST trial was a randomized trial of 458 patients evaluating capcitabine and cisplatin (CX) for six cycles versus CX for two cycles, CRT with capcitabine (XRT) to 45 Gy, followed by CX for two more cycles (CX/XRT/CX) for patients with margin-negative gastric cancer and a D2 lymph node dissection. All patients had a D2 lymph node dissection, with a median of 40 lymph nodes evaluated per patient. Patients were at high risk for both local and distant failure, with more than 85% enrolled having involved lymph nodes. More than 75% of patients completed the full course of therapy as planned. Although there was no significant difference in the primary endpoint of 3-year DFS with the addition of radiation (78.2% in the CX/XRT/CX arm vs. 74.2% in the CX arm; p = .0862), there was a significant improvement in DFS for patients with involved lymph nodes who received CRT (77.5% in the CX/XRT/CX arm vs. 72.3% in the CX arm; p = .0365). There were low rates of locoregional recurrence in both arms (4.8% in the CX/XRT/CX arm vs. 8.3% in the CX arm; p = .3533). The ARTIST-II trial is currently planned to assess the role of CRT in addition to chemotherapy for patients with node-positive gastric cancer after R0 resection and D2 lymph node dissection (NCT01761461).

Although the subgroup analysis from the ARTIST trial would suggest that patients with involved lymph nodes benefit from adjuvant chemoradiation in addition to chemotherapy, it is unclear whether these results can be extrapolated to a Western population. Gastric cancer outcomes are significantly superior in Eastern patient populations: 3-year DFS in the surgery-alone arms of the ACTS-GC and CLASSIC trials was 59%, compared with approximately 30% in the surgery-alone arms of the Intergroup 0116 and MAGIC trials. Although some of these differences may be attributed to more extensive nodal dissections, this difference in outcomes is also seen for patients with unresectable or metastatic disease. For example, in the AVAGAST trial of bevacizumab in addition to CX in advanced gastric cancer, Asian patients had the highest median survival in the chemotherapy-alone arm (12.1, 8.6, and 6.8 months for Asian, European, and Pan-American patients, respectively) and the highest response rate to chemotherapy.

For Western patients, the CRITICS trial evaluated perioperative chemotherapy versus preoperative chemotherapy and adjuvant CRT for 788 patients with resectable gastric adenocarcinoma. After three cycles of preoperative chemotherapy, approximately 94% of patients in the chemotherapy-alone arm and 93% of patients in the postoperative CRT arm underwent resection, with rates of R0 resection of 80% and 84%, respectively. Information on the extent of nodal dissection is not yet available. However, only approximately 60% of patients were able to start postoperative treatment, and only 47% of patients in the chemotherapy arm and 52% of patients in the postoperative CRT arm were able to complete treatment as planned. There was no significant difference in OS between the two cohorts, with 5-year OS of 40.9% with chemotherapy alone and 40.8% with chemotherapy followed by CRT. With less than 50% of patients completing the full course of planned treatment, the CRITICS trial underscores the inherent challenges associated with delivery of postoperative treatment after gastrectomy and provides further support for ongoing efforts to shift treatment to the neoadjuvant setting.

The large treatment radiotherapy fields needed to encompass regional nodal basins after gastrectomy make postoperative chemoradiation particularly challenging to deliver (Figs. 1 and 2). Based on the resulting toxicity seen in the adjuvant setting as well as the excellent outcomes seen with neoadjuvant CRT in esophageal and EGJ cancer, there is growing interest in preoperative CRT for patients with gastric cancer. There are no mature randomized data in distal gastric cancers, but completed trials in distal esophageal and EGJ cancer show impressive outcomes. The POET trial randomly assigned patients with T3/T4 adenocarcinoma of the distal esophagus or gastric cardia to 2.5 cycles of neoadjuvant cisplatin, 5-FU, and leucovorin versus two cycles of neoadjuvant cisplatin, 5-FU, and leucovorin followed by chemoradiation to 30 Gy and one cycle of cisplatin and etoposide followed by resection. Although the study terminated early as a result of poor accrual, enrolling 119 of an expected 354 patients, there was a trend toward improvement in 3-year OS with CRT (47.4% vs. 27.7%; p = .07). Five-year follow-up showed a significant improvement in local progression-free survival after CRT. In addition, there was a significant increase in the rates of pathologic complete response (15.6% vs. 2.0%) and N0 resections (64.4% vs. 37.7%) with CRT.

In the CROSS trial, 368 patients with resectable T1 to T3 or node-positive esophageal or EGJ cancer (75% adenocarcinoma, 23% squamous cell carcinoma) were randomly assigned to...
receive upfront resection versus neoadjuvant chemoradia-
tion to 41.4 Gy with weekly carboplatin and paclitaxel fol-
lowed by resection. There were significant improvements
in rates of complete resection, pCR, and OS with neoadju-
vant CRT, thereby establishing neoadjuvant CRT followed
by resection as a standard of care for patients with distal
esophageal and EGJ cancer. Neoadjuvant CRT was associated
with not only an improvement in rates of complete resec-
tion (92% vs. 69%; p < .001) but also an overall pCR rate of
29%. The pCR rate varied by histology, with a 49% pCR rate
in squamous cell carcinoma and a 23% pCR rate in adeno-
carcinoma. Median OS was doubled (49.4 vs. 24 months),
and 5-year OS increased by 13% (47% vs. 24%; p < .001).
Importantly, neoadjuvant treatment was well tolerated and
was not associated with an increase in postoperative mor-
bidity compared with resection alone (p = .85).
In gastric cancer, neoadjuvant CRT has thus far been ex-
plored in single-arm phase I and II trials. RTOG 9904 was
a phase II single-arm trial of inducƟ on chemotherapy with
two cycles of 5-FU, leucovorin, and cisplatin followed by
preoperative CRT and resection. A total of 49 patients
with resectable gastric adenocarcinoma were enrolled, and
43 were evaluable; 77% of paƟ  ents underwent R0 resec-
tion and 50% underwent a D2 lymph node dissecƟ  on. The

![FIGURE 1. Sample Digitally Reconstructed Radiograph of the Treatment Fields for a Preoperative Patient (Left) and a Postoperative Patient (Right)](image1)

![FIGURE 2. Sample Radiotherapy Plans for the Treatment of Neo-/Adjuvant EGJ Cancers](image2)

These sample radiotherapy plans for the treatment of a neoadjuvant EGJ cancer (upper 3 images) and an adjuvant EGJ cancer (lower 3 images), demonstrate the larger treatment fields in the adjuvant setting. In the lower 3 panels, the left panel shows the anastomosis, whereas the centre and right panels show coverage of the regional lymph node basins, including the perigastric lymph nodes.
pCR rate was 26%. Median OS was 23.2 months, with an improved rate of 1-year OS in patients with a pCR (82% vs. 69%). A Dutch phase I/II single-arm trial of chemoradiation to 45 Gy with weekly carboplatin and paclitaxel enrolled 35 patients with clinical T3 or T4 gastric cancer.44 One patient developed progressive disease, and the remaining patients were all able to undergo resection. The R0 resection rate was 72%, the pCR rate was 16%, and the near complete response rate was 24%. The rate of R0 resection in this trial was particularly impressive, considering that eight of 12 patients who were initially considered to be unresectable had a R0 resection after CRT. Importantly, both of these trials as well as other phase I and II trials have demonstrated that neoadjuvant CRT is feasible for patients with locally advanced gastric cancer and is not associated with increased operative morbidity.46-48 Furthermore, although the numbers remain small, the rates of pathologic complete response seen in several of these trials are similar to those seen in the CROSS trial and have also been associated with improved OS on multivariate analysis.47,48

Randomized phase III trials are ongoing. The TOPGEAR trial will randomly assign a planned total of 752 patients with resectable gastric cancer to perioperative chemotherapy versus induction chemotherapy, neoadjuvant CRT, and postoperative chemotherapy.49 The CRITICS-II trial will randomly assign patients to receive preoperative chemotherapy, CRT, or combined chemotherapy and CRT (NCT02931890), and the ESOPEC trial will randomly assign a planned 438 patients with esophageal and EGJ adenocarcinoma to receive perioperative FLOT chemotherapy versus neoadjuvant (CROSS protocol) CRT (NCT02509286).

TARGETED THERAPIES IN EARLY-STAGE ESOPHAGOGASTRIC CANCER

Targeted therapies with antiangiogenic and HER2-directed monoclonal antibodies form part of the established treatment paradigm in advanced esophagogastric cancer.50-53 In early-stage disease, results have been inconsistent and clinical trials are ongoing to establish the role of anti-VEGF– and anti-HER2–directed therapies in this setting. The MRC phase II/III ST03 trial showed no additional benefit to perioperative ECX with the addition of bevacizumab, the monoclonal antibody against VEGF.11 This trial reported that of 1,063 patients with resectable esophagogastric adenocarcinoma, there was no improvement in OS among patients randomly assigned to receive bevacizumab with three cycles of perioperative ECX and an additional six cycles (every 21 days) of maintenance on completion of chemotherapy compared with the chemotherapy alone. Furthermore, postoperative anastomotic leaks and wound-healing complications were higher in the bevacizumab group; therefore, perioperative chemotherapy plus bevacizumab is not recommended. The phase II/III RAMSES trial (NCT02661971) is currently investigating perioperative FLOT with or without the anti-VEGFR2 monoclonal antibody ramucirumab. In HER2-positive gastric and EGJ adenocarcinoma, trastuzumab with perioperative chemotherapy (NCT01130337), CRT (NCT01748773), and in combination with pertuzumab with perioperative chemotherapy (NCT02205047) is under investigation (Table 1).

BIOMARKERS IN ESOPHAGOGASTRIC CANCER

Response rates to treatment in esophagogastric cancer vary and even patients with similar-stage disease may have different outcomes. Putative prognostic and predictive biomarkers are under investigation with the aim to identify subsets of patients who are likely to benefit from a specific therapy, thereby optimizing treatment selection and improving survival for individual patients.

The pathologic T stage and the Mandard tumor regression grade (TRG) are important predictors of survival in resected esophagogastric cancer. In an analysis of 584 consecutive esophageal and EGJ adenocarcinoma resection specimens, among which 400 patients had received neoadjuvant chemotherapy, from two high-volume U.K. cancer centers, prognosis was found to be determined by pathologic stage rather than clinical stage.54 In this analysis, tumor downstaging was shown to be the strongest independent predictor of survival following adjustment for other prognostic factors. For patients who responded to neoadjuvant chemotherapy, lower rates of local and systemic recurrence and improved Mandard TRGs were observed (6% vs. 13%; p = .030) compared with nonresponders (19% vs. 29%; p = .027).54 In a retrospective analysis of 330 patients in the MRC MAGIC trial, TRG was predictive for OS where the median OS was 20.5 months for patients with TRGs 3 to 5, whereas the median OS in patients with TRGs 1 and 2 was not reached. High TRGs and lymph node metastases were negatively associated with survival on univariate analysis, although lymph node metastases alone was independently predictive of survival on multivariate analysis.55 In the MRC ST03 trial, Mandard grades 1 and 2 had a significantly improved 3-year survival compared with Mandard grades 3 to 5 or no resection (HR 0.30; 95% CI, 0.21–0.44; p ≤ .0001).56 An adaptive trial design based on pathologic tumor stage or Mandard TRG, such that patients with adverse prognostic features are assigned to receive intensified treatment, is an area of potential future research.

In a series of early prospective trials, change in tumor metabolic activity assessed by PET/CT during preoperative chemotherapy for patients with EGJ and gastric adenocarcinoma was predictive for tumor response, prognosis, and recurrence.57-59 A subsequent phase II clinical trial with 119 patients with locally advanced type 1 and 2 EGJ adenocarcinoma assigned all patients to 2 weeks of platinum/5-FU–based induction chemotherapy followed by evaluation of metabolic response by PET/CT. Metabolic response was predefined as a decrease in glucose standard uptake value of 35% or greater. Responding patients continued to receive neoadjuvant chemotherapy for 12 weeks and then proceeded to surgery, and nonresponders proceeded straight to surgery. After a median follow-up of 2.3 years, the median OS was not met in metabolic responders and was 25.8 months (19.4–32.2 months) in nonresponders (p = .015).59 The subsequent MUNICON II study was a prospective trial to investigate
### TABLE 1. Selected Current Clinical Trials With Anti-VEGF, Anti-HER2, and Anti–PD-1/PD-L1 Therapies in the Perioperative, Neoadjuvant, and Adjuvant Settings

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
<th>Phase</th>
<th>Trial Title</th>
<th>Population</th>
<th>Treatment Arms</th>
<th>Planned Recruitment (No. of Patients)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perioperative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02661971</td>
<td>II/III</td>
<td>Perioperative ramucirumab in combination with FLOT versus FLOT alone for resectable esophagogastric adenocarcinoma: RAMSES—a phase II/III trial of the AIO</td>
<td>Gastric/EGJ</td>
<td>FLOT vs. FLOT and ramucirumab</td>
<td>908</td>
<td>Phase II: pCR/pSR; phase III: OS</td>
</tr>
<tr>
<td>NCT01130337</td>
<td>II</td>
<td>An open-label, multicenter study to evaluate the DFS rate of a perioperative combination of capecitabine, trastuzumab, and oxaliplatin in patients with resectable gastric or gastroesophageal junction adenocarcinoma</td>
<td>HER2-positive gastric/EGJ</td>
<td>CAPOX and trastuzumab</td>
<td>36</td>
<td>DFS</td>
</tr>
<tr>
<td>NCT02205047</td>
<td>II</td>
<td>Integration of trastuzumab, with or without pertuzumab, into perioperative chemotherapy of HER2-positive stomach cancer: the INNOVATION trial</td>
<td>HER2-positive gastric/EGJ</td>
<td>CX/5-FU vs. CX/5-FU and trastuzumab vs. CX/5-FU, trastuzumab, and pertuzumab</td>
<td>220</td>
<td>Near pCR rate</td>
</tr>
<tr>
<td>NCT03221426</td>
<td>III</td>
<td>A phase III, randomized, double-blind, clinical trial of pembrolizumab (MK-3475) plus chemotherapy versus placebo plus chemotherapy as neoadjuvant/adjuvant treatment for subjects with gastric EGJ adenocarcinoma (KEYNOTE-585)</td>
<td>Gastric/EGJ</td>
<td>CX/5-FU and placebo vs. CX/5-FU and pembrolizumab</td>
<td>860</td>
<td>OS/EFS/pCR rate/AEs</td>
</tr>
<tr>
<td>NCT03399071</td>
<td>II</td>
<td>Perioperative immunochemotherapy in operable esophageal and gastric cancer (ICONIC)</td>
<td>Gastric/esophageal</td>
<td>FLOT and avelumab</td>
<td>40</td>
<td>pCR rate</td>
</tr>
<tr>
<td><strong>Neoadjuvant</strong></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>NCT02735239</td>
<td>I/II</td>
<td>Phase I/II study of anti–PD-L1 in combination with chemo(radio)therapy for esophageal cancer</td>
<td>Cohorts C and D: esophageal/EGJ followed by postoperative chemotherapy or CRT</td>
<td>Durvalumab</td>
<td>75 cohorts A to D</td>
<td>AEs, DLT</td>
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<tr>
<td><strong>Adjuvant</strong></td>
<td></td>
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<tr>
<td>NCT01748773</td>
<td>II</td>
<td>Safety and tolerability of oxaliplatin-capecitabine-trastuzumab combination and chemoradiotherapy in operated patients with HER2-positive gastric or gastroesophageal junction adenocarcinoma: phase II study TOXAG</td>
<td>Resected HER2-positive gastric/EGJ</td>
<td>CAPOX, trastuzumab, and 45 Gy in 25 fractions</td>
<td>35</td>
<td>AEs, PS</td>
</tr>
<tr>
<td>NCT02743494</td>
<td>III</td>
<td>A randomized, multicentre, double-blind, phase III study of adjuvant nivolumab or placebo in subjects with resected esophageal or EGJ cancer (CheckMate 577)</td>
<td>Resected esophageal/EGJ</td>
<td>Nivolumab vs. placebo</td>
<td>760</td>
<td>DFS/OS</td>
</tr>
<tr>
<td>NCT03006705</td>
<td>III</td>
<td>A multicenter, double-blind, randomized study of patients with gastric cancer undergoing postoperative adjuvant chemotherapy (ONO-4538)</td>
<td>Resected gastric/EGJ</td>
<td>CAPOX or S1 and nivolumab vs. CCAPOX or S1 and placebo</td>
<td>700</td>
<td>RFS</td>
</tr>
</tbody>
</table>

Abbreviations: FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; EGJ, esophagogastric junction; pCR, pathologic complete response; pSR, pathologic subtotal response; OS, overall survival; DFS, disease-free survival; CAPOX, capcitabine and oxaliplatin; CX, cisplatin and capcitabine; 5-FU, 5-fluorouracil; EFS, event-free survival; AE, adverse event; CRT, chemoradiotherapy; DLT, dose-limiting toxicity; PS, performance status; RFS, relapse-free survival.
whether nonresponders who underwent early PET/CT would benefit from preoperative salvage neoadjuvant radiotherapy compared with continuation with neoadjuvant chemotherapy alone with a primary endpoint of R0 resection rate. Fifty-six patients with locally advanced EGI adenocarcinoma were included in the study and although the nonresponders showed improved histopathologic response, the primary endpoint of increased R0 resection rate was not met. Therefore, for poor metabolic responders, proceeding directly to surgery or receiving radiotherapy with similar cytotoxic drugs did not salvage these patients.

Further studies have subsequently investigated whether chemotherapy and radiotherapy treatments can be adapted based on early PET/CT response to drive response in PET/CT metabolic nonresponders. The AGITG DOCTOR trial, a randomized phase II trial of 150 patients with resectable gastric and EGI adenocarcinoma, assigned all patients to receive one cycle of CF prior to PET/CT evaluation. Patients with a 35% or greater reduction in the maximum standard uptake value were classified as early metabolic responders and continued with a second cycle of CF followed by surgery. Patients classified as nonresponders were randomly assigned 1:1 to CF plus docetaxel for two cycles or to CF plus docetaxel with concurrent 45-Gy radiotherapy with a primary endpoint of histologic response. A major histologic response (<10% residual tumor) was reported for three of 45 patients (7%) with early metabolic response, six of 30 patients (20%) treated with CF plus docetaxel, and 22 of 35 patients (63%) treated with CF plus docetaxel radiotherapy, demonstrating that docetaxel in addition to preoperative chemotherapy and CRT can induce high rates of histologic response. In the CALGB 80803 trial, 257 patients with resectable esophageal and EGI adenocarcinomas were randomly assigned to one of two arms of induction chemotherapy followed by PET/CT (performed on days 36–42); PET responders (≥35% reduction in the maximum standard uptake value) continued on the same chemotherapy with concurrent radiotherapy (50.4 Gy in 28 fractions) and nonresponders were crossed over to alternative chemotherapy with concurrent radiotherapy. The efficacy criteria were met for improvement in pathologic complete response rates for patients who were PET nonresponders after induction chemotherapy and received alternative chemotherapy during CRT. Although the survival data are awaited, these studies show that stratifying treatment based on metabolic response on PET/CT is feasible, although the use of PET as a biomarker to modulate early treatment is yet to be fully established.

In HER2-overexpressed esophagogastric cancer, HER2 is a clinically significant therapeutic target. However, the value of HER2 as a prognostic and predictive biomarker remains to be confirmed. A retrospective analysis of patients enrolled in the INT-0116/SWOG9008 trial reported a significant interaction between HER2 amplification and treatment in terms of DFS (p = .020) and OS (p = .034). Among the 148 evaluable patients, the median OS improved from 24 months in the surgery-alone arm to 44 months with postoperative chemoradiation in patients with HER2-nonamplified tumors (p = .003). For patients with HER2-amplified tumors, there was no significant difference in OS with postoperative chemoradiation compared with surgery alone. The results suggesting that the benefit of postoperative chemoradiation in resectable gastric and EGI tumors are limited to HER2-negative tumors. However, retrospective analysis of the ACTS-GC trial population showed that HER2 status did not affect DFS or OS and there was no interaction between S1 and HER2 on survival. Similarly, HER2 expression had no effect on DFS in the ARTIST trial, and HER2 expression was not associated with DFS or OS in a prospective series of 117 patients with Epstein-Barr virus (EBV)–associated gastric cancer.

Esophagogastric cancers exhibit a high degree of molecular heterogeneity. Work carried out using microarray-based gene expression profiling to identify new molecular subtypes in gastric cancer subtypes identified two major genomic subgroups (G-INT and G-DIF), which were independently prognostic of survival and demonstrated differential benefit from adjuvant 5-FU in retrospective patient cohorts. In vitro, the G-INT lines were more sensitive to 5-FU and oxaliplatin than the G-DIF cell line but were also more resistant to cisplatin. A subsequent phase II study of 74 patients with locally advanced, metastatic, and recurrent gastric cancer integrated a pretreatment biopsy from which patients were allocated to receive S1/oxaliplatin or S1/cisplatin based on their genomic profiles (NCT01100801). Based on the intercurrent work published by Lei et al identifying three intrinsic gastric cancer subtypes (mesenchymal, proliferative, and metabolic), post hoc genomic classification was performed. A significantly higher observed objective response rate was seen for patients assigned to receive S1/oxaliplatin based on their genomic profile compared with S1/cisplatin (44.8% vs. 8.3%; p = .033). The median turnaround time for genomic results was 7 working days (interquartile range, 5–9 days), demonstrating that molecular profiling to direct choice of chemotherapy can be performed within a reasonable timeframe and provide proof of concept for tailoring chemotherapy to different molecular subtypes. Although genomic classifiers have shown some promising results, further investigation is required to establish the role this approach may play in the management of early-stage disease.

The landmark article published by The Cancer Genome Atlas Research Network reporting the results of a comprehensive molecular analysis of 295 gastric cancers described four different gastric cancer subtypes: EBV positive (9%), microsatellite instability (MSI; 22%), genomically stable (20%) and chromosomal instability (50%). Expanded analysis of these subgroups has identified potential therapeutic opportunities. Approximately 15% of EBV-positive tumors have genomic amplification of the chromosomal region 9p24.1, which encodes the PD-1 ligands. Furthermore, EBV-positive cancers have PD-L1 expression in tumor cells (50%; 16 of 32) not seen in other gastric cancer subtypes and this is not restricted to gastric cancer with amplification of 9p24.1, suggesting more than one mechanism for inducing PD-L1
expression in this subgroup. Among EBV-negative gastric cancers, MSI gastric cancers also have expression of PD-L1 in tumor cells (33%) and immune cells (45%). By contrast, in EBV-negative and microsatellite stable (MSS) gastric cancers, PD-L1 expression was not observed in tumor cells, although 35% of patients with EBV-negative/MSI gastric cancer exhibit PD-L1 expression of inflammatory cells. Moreover, an interferon-γ gene signature, a proposed marker of sensitivity to PD-1 therapy, is enriched in EBV-positive and MSI gastric cancer, further suggesting that these subgroups of patients with gastric cancer may respond to checkpoint inhibition. Given the current intense interest in immune checkpoint inhibitors in esophageal gastric cancers, potential predictive biomarkers of response are of significant notice and translational protocols of PD-1 and PD-L1 agents in combination with chemotherapy are likely to focus on this area of research.

MSI and mismatch repair deficiency are prognostic for survival in many cancers. Secondary analysis of 303 patients with MSI results available from the MRC MAGIC trial showed that 20 of 303 patients had MSI-high (H) tumors. Mismatch repair deficiency and MSI-H were associated with a positive prognostic effect among patients treated with surgery alone, such that the median OS was not reached for patients with MSI-H tumors (95% CI, 4.4 months—not reached) compared with a median OS of 20.3 months (95% CI, 16.7–22.7 months; HR 0.35; 95% CI, 0.11–1.11; p = .08) for patients with MSS and MSI-low tumors. However, for patients treated with perioperative chemotherapy conversely, the median OS for patients with mismatch repair deficiency or MSI-H tumors was 9.6 months compared with 19.5 months for patients who had neither mismatch repair deficiency or MSI-H (HR 2.18; 95% CI, 1.08–4.42; p = .03), demonstrating a differentially negative prognostic effect for patients treated with chemotherapy. A retrospective analysis of the CLASSIC trial showed that in 592 specimens, a similar proportion (6.1%) were MSI-H. Among the patients treated with surgery alone, MSI-H had an improved 5-year DFS adjusted for age, sex, tumor grade, disease stage, and location compared with MSI-low or MSS (HR 0.244; 95% CI, 0.069–0.867; p = .0292). However, as seen in the MAGIC analysis, for patients treated with chemotherapy, while DFS was improved for patients with MSI-low or MSS tumors, no benefit was seen in the MSI-H group. Although not yet fully elucidated, assessment of MSI is available at the clinical level and there may be a future role for MSI on preoperative biopsy to select patients for perioperative or adjuvant chemotherapy. However, the majority of tumors are MSS and considerable research effort is being engaged currently, with several randomized controlled trials investigating the role of immunotherapy in resectable esophageal gastric cancer (Table 1).

CONCLUSION

It is evident that although a multimodal approach to the treatment of operable esophageal gastric cancer has improved prognosis, overall the outlook remains poor and further advances are needed to improve survival for these patients. The role of targeted agents in this setting is being evaluated and the results of the RAMSES trial investigating perioperative FLOT with or without ramucirumab are awaited. The TOPGEAR, ARTIST-II and CRITICS-II trials will provide valuable information on the optimal role of CRT in resectable gastric cancer. Currently, there are no validated biomarkers in early-stage esophageal gastric cancer; however, candidate imaging, pathologic, and molecular biomarkers are being evaluated in clinical trials. Incorporation of validated prognostic and predictive biomarkers in the treatment of operable esophageal gastric cancer is hoped to stratify and optimize patient treatment selection in the future.

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N euroendocrine neoplasms (NENs) represent a heterogeneous group of neoplasms arising from the diffuse neuroendocrine cell system. Although these tumors can originate anywhere in the body, they primarily arise in either the lung or gastroenteropancreatic (GEP) tract. For many patients, the disease can display a less aggressive biology compared with other solid tumors, growing slowly over a period even of many years. Despite their rarity, the incidence and prevalence of neuroendocrine tumors (NETs) is rising, and NETs are now the second most prevalent advanced gastrointestinal cancer after colorectal cancer.\(^1,2\) In recent years, important strides have been made in drug development, following the completion of rigorous phase III clinical trials.\(^3-7\) This burgeoning interest in NET clinical research has occurred in parallel with advances in NET translational medicine—specifically, an improvement in our understanding of the genetics through use of sequencing technology. Although few actionable alterations have been identified, sequencing can provide important information that can be used in concert with NET pathologic classification for disease prognostication and treatment decisions.

In this review, we will discuss current NET classification and available drug therapies, recent advances in NET translational medicine, use of radiolabeled therapies for NETs, and best practices for sequencing the available systemic treatments.

**PATHOLOGY**

The World Health Organization (WHO) GEP-NEN pathologic classification is a pivotal tool to predict tumor behavior. The WHO criteria classify NENs by cell architecture (well and poorly differentiated) and proliferative index as measured by Ki-67 and/or mitotic count (grade 1, low; grade 2, intermediate; and grade 3, high).\(^8\) Well-differentiated NENs are defined as “tumors” (NETs), whereas poorly differentiated NENs are defined as neuroendocrine “carcinomas” (NECs). To date, the WHO classification system has been the most important prognostic tool. However, there are limitations with the classification schema particularly with respect to the grade 3 category, because more recent data demonstrate distinct patterns of response to treatment as well as divergent outcomes for grade 3 NETs compared with grade 3 NECs. In a study of both well- and poorly differentiated grade 3 GEP-NENs, poorer response rates (despite longer survival) to platinum-based chemotherapy were observed in NETs with a Ki-67 proliferation index in the lower end of the grade 3 range (≤ 55%).\(^9\) These findings were corroborated in a subsequent study of 45 patients with grade 3 well- and poorly differentiated pancreatic NENs, in which inferior overall survival (OS) was observed in NECs, despite a higher response to platinum drugs; interestingly, similar response rates to alkylating agents were seen in both NETs and NECs.\(^10\) Through these studies and others, there is growing recognition that the WHO grade 3 category contains both NECs and NETs.\(^11-13\) With this understanding, the 2017 WHO criteria for pancreatic NENs now recognize both well- and poorly differentiated cohorts within the grade 3 category, an important pathologic distinction for the treating clinician to recognize.\(^14\)

**NET MOLECULAR BASIS**

Advances in our understanding of the molecular basis of NETs now provide information to be used in concert with traditional pathologic criteria.

The initial landmark whole-exome study sequenced 10 well-differentiated pancreatic NET (pNET) samples, and the most commonly mutated genes were then screened in an additional 58 tumors.\(^15\) The cohort was a mix of early-stage
(59%) and metastatic (41%) tumors. The study investigators observed more mutations in genes implicated in chromatin remodeling (MEN1, DAXX, and ATRX) as well as those along the mTOR pathway (largely in PTEN and TSC2). Importantly, in this study, a survival benefit was noted for those patients whose tumors harbored mutations in both MEN1 and either DAXX or ATRX (100% OS at 10 years); in the absence of this mutation status, 60% of patients died within 5 years of diagnosis.

A subsequent retrospective evaluation used a combination of immunohistochemistry testing as well as targeted exomic sequencing with a narrow gene panel in pancreatic primary grade 1/grade 2 NETs and poorly differentiated NECs. In this series, loss of DAXX and ATRX staining was noted only in well-differentiated NETs, whereas staining was intact in all poorly differentiated NECs. In addition, exomic and immunohistochemistry alterations were noted in RB1 and TP53 in poorly differentiated NECs, with no changes noted in these genes or in protein expression in well-differentiated NETs. These findings were further corroborated in other studies, and it is now well recognized that alterations in RB1 and TP53 are largely restricted to poorly differentiated NECs.

More recently, whole-genome sequencing was performed in 102 primary pNETs (18.4% with metastatic disease). Four pathways (chromatin remodeling, DNA damage repair, mTOR, and telomere maintenance) were identified as commonly altered. In addition, previously unreported germline mutations were identified in DNA repair genes (MUTYH, CHEK2, and BRCA2), suggesting a greater than expected germline component for pNET pathogenesis.

Exome sequencing has also been pursued in small intestine NETs. In the largest analysis, 48 small intestine NETs (70% grade 1, 30% grade 2) were sequenced and 14 mutations in splice sites were identified; in an integrated analysis, recurrently altered genes implicated in chromatin remodeling, DNA damage, apoptosis, renin-angiotensin system signaling, and axon guidance were noted, with alterations most frequently seen along the mTOR pathway.

Next-generation sequencing provides the opportunity to bring these translational efforts into the routine practice setting, allowing clinicians the opportunity to prospectively perform molecular testing while providing clinical care to patients. Recent clinical next-generation sequencing efforts in NETs are ongoing; to date, findings in well-differentiated pNETs have been consistent with prior investigation, demonstrating frequent alterations in the chromatin remodeling factors and in the mTOR pathway.

**NET THERAPY: KEY ADVANCES THROUGH LEVEL 1 EVIDENCE**

In the past decade, as our understanding of the NET molecular basis has improved, the NET treatment paradigm has changed as a result of the completion of several prospective clinical trials leading to practice-changing outcomes.

**Somatostatin Analogs**

Because the majority of well-differentiated NETs (approximately 80%) express somatostatin receptor subtype 2 (SSTR-2) on their surface, the therapeutic role of synthetic somatostatin analogs (SSAs; octreotide and lanreotide) has been investigated. These efforts have demonstrated a clear role for SSAs in the treatment of symptoms related to hormone secretion in functional NETs. Additional investigation has also demonstrated a role for both octreotide and lanreotide in tumor cytostatic control. In the phase III CLARINET study of 85 patients with midgut NETs, a significant difference in time to progression was noted during treatment with 30 mg of octreotide long-acting release (LAR) monthly versus placebo (median, 14.3 vs. 6 months; p < .001). The CLARINET study was subsequently conducted and included a broader population of 204 patients with well- or moderately differentiated grade 1 or grade 2 (Ki-67 < 10%) enteropancreatic NETs. In the CLARINET study, patients were randomly assigned to receive 120 mg of lanreotide monthly or placebo, and the study investigators observed significantly prolonged progression-free survival (PFS) with lanreotide compared with placebo (median, not reached vs. 18 months; p < .001). The National Comprehensive Cancer Network guidelines recommend either octreotide or lanreotide as first-line choices for symptom and/or tumor control.

**Targeted Drugs**

Both single and combination therapies of the multitargeted receptor tyrosine kinase inhibitor sunitinib and the mTOR inhibitor everolimus have been tested in clinical trials of NETs. In 2011, through the conduct of two phase III clinical trials, roles for both sunitinib and everolimus were demonstrated in pNETs, with subsequent investigation demonstrating a role for everolimus in lung and other gastrointestinal NETs.
Based on phase II data demonstrating antitumor activity for sunitinib in pNETs (but not in NETs of other sites of origin), Raymond et al carried out a phase III trial of 171 patients with advanced and progressive well-differentiated pNETs. In this study, patients were randomly assigned to receive 37.5 mg of sunitinib daily or placebo. The study showed a significant PFS benefit with sunitinib compared with placebo (median PFS, 11.4 vs. 5.5 months) and was terminated early after investigators observed more serious events and deaths in the placebo arm. The findings from this study, taken together, led the U.S. Food and Drug Administration to approve sunitinib for treatment of pNETs.

Phase II studies of everolimus demonstrated promising data in NETs originating within and outside of the pancreas. With this foundation, the phase III RADIANT-3 study was conducted, in which a significant improvement was noted in PFS among patients with well-differentiated grade 1/2 progressive pNETs randomly assigned to receive either 10 mg of everolimus daily or placebo (PFS, 11.0 vs. 4.6 months); based on these findings, the U.S. Food and Drug Administration approved everolimus for the treatment of pNETs.

RADIANT-2, a phase III study of treatment with 10 mg of everolimus daily plus 30 mg of octreotide LAR monthly versus placebo plus 30 mg of octreotide LAR monthly, was then conducted among 429 patients with advanced NETs who had a history of carcinoid syndrome. Based on this eligibility criterion, the tumor type consisted predominantly of midgut NETs. Although median PFS was longer with everolimus compared with placebo (16.4 vs. 11.3 months), the result fell short of significance. Moreover, there was a nonsignificant trend toward reduced OS with everolimus in this study. Subsequently, RADIANT-4, a phase III study of treatment with 10 mg of everolimus daily versus placebo in advanced nonfunctional NETs of gastrointestinal or lung origin, was conducted. In RADIANT-4, a significant PFS benefit was seen for everolimus versus placebo (median, 11.0 vs. 3.9 months); based on these findings, the U.S. Food and Drug Administration approved everolimus for the treatment of advanced NETs of lung or gastrointestinal origin.

Cytotoxic Chemotherapy

Cytotoxic chemotherapy is typically used in NECs and in NETs of higher tumor grade, heavy tumor burden, and/or a more aggressive clinical course. An initial role for chemotherapy in NEN management dates back to the 1960s, with the earliest investigations of streptozocin-based chemotherapy for progressive and advanced pNETs. Over the years, a role for both alkylating (streptozocin, temozolomide, and dacarbazine) and platinum chemotherapy drugs has been demonstrated, primarily in pNETs; in particular, studies of alkylating therapies in pNETs, both retrospective and prospective, have reported objective response rates (ORRs) as high as 45% to 70%.

NUCLEAR MEDICINE AND PEPTIDE RECEPTOR RADIONUCLIDE THERAPY IN NETS

Although SSAs remain the cornerstone first-line treatment option for most patients with advanced, unresectable NETs based on their exceptionally favorable safety profile and their ability to inhibit tumor progression and palliate hormonal symptoms, most patients eventually experience disease progression while receiving first-line SSA treatment. Radiolabeled SSAs, a form of peptide receptor radionuclide therapy (PRRT), have emerged as an effective option for patients with SSTR-expressing tumors. The underlying principle of this treatment is rather simple: by attaching a radionuclide to an SSA, targeted radiation can be delivered systemically to tumors.

Radiolabeled SSAs consist of a carrier molecule (the SSA), a radionuclide isotope, and a chelator that binds and stabilizes the complex. Tetra-azacyclododecane-tetra-acetic acid (DOTA) and diethylenetriamine penta-acetic acid have been the most commonly used chelators. Examples of SSAs include either octreotide or octreotide, an analog with slightly enhanced binding affinity to SSTR-2. The term “DOTATOC” is used when a DOTA chelator is combined with octreotide, whereas “DOTATATE” denotes the combination of DOTA with octreotide. The first-generation radionuclide used in PRRT was 111In, a gamma-emitting isotope that also emits Auger electrons with short particle range resulting in a weak cytotoxic effect. Subsequent generations of radionuclide isotopes have included 90Y and 177Lu, both beta-emitting isotopes. The intermediate-range tissue penetration of 177Lu (approximately 2 mm) results in a relatively favorable therapeutic index. Because radiolabeled SSAs target the SSTR, virtually all studies of this treatment have required evidence of tumoral SSTR expression on SSTR imaging.

Until recently, most studies evaluating radiolabeled SSAs consisted of prospective registries or small single-arm studies and institutional retrospective databases. Differences in eligibility criteria, response criteria, and treatment doses render comparisons difficult. It is also important to note that not all studies have required disease progression at baseline. ORRs to 90Y-DOTATOC have ranged from less than 10% to greater than 30%, and median durations of PFS have varied from 17 to 29 months. In one multicenter study of 90 patients with refractory carcinoid syndrome treated with three cycles of 90Y-DOTATOC, a stable disease rate of 70% was observed but the ORR was only 4%, which is likely attributable to the population studied (primarily midgut NETs) and heavy pretreatment. A higher response of 23% was observed in a single-arm phase II study using four cycles of 90Y-DOTATOC in a more heterogeneous population of GEP and lung NETs.

Somewhat more promising response rates and PFS durations have been observed with 177Lu-based radiolabeled SSAs. Since 2000, more than 1,200 patients have been treated at the Erasmus Medical Center in Rotterdam, the Netherlands, using a standard protocol of 200 mCi (7.4 GBq) of 177Lu-DOTATATE intravenously every 8 weeks for four treatments. Dutch nationals followed a standard, prospectively defined evaluation program allowing for accurate assessment of outcomes. Efficacy data on 443 Dutch patients with GEP and lung NETs were recently reported, demonstrating an ORR of 39%, median PFS of 29 months, and median
OS of 63 months. An ORR of 31% was observed in midgut NETs, with a median PFS of 30 months. Patients with pNETs had an ORR of 55%, also with a median PFS of 30 months. Response rates ranging from 30% to 42% were seen in other categories of GEP and lung NETs. Other studies have yielded similar results: for example, a phase I to II trial of 51 patients with advanced NETs treated with 177Lu-DOTATATE reported an ORR of 33%, with a median time to progression of 36 months. In addition to radiographic outcomes, several studies have shown notable enhancement in quality of life with 177Lu-DOTATATE treatment, along with improvements in hormonal syndrome-associated symptoms.

Acute and subacute side effects associated with PRRT include cytopenias, caused by irradiation of the bone marrow. Grade 3 or 4 neutropenia and thrombocytopenia events occur for approximately 5% of patients treated with 177Lu-DOTATATE, with nadir counts commonly occurring 4 to 6 weeks after each infusion and resolving within 8 weeks. Nephrotoxicity is a side effect that is primarily associated with 90Y-associated treatments and can be significantly ameliorated with infusion of positively charged amino acids such as arginine or lysine. Indeed, with use of 177Lu-based PRRT and amino acid prophylaxis, the risk of long-term severe treatment-related nephrotoxicity is negligible.

The most serious long-term toxicity associated with PRRT is irreversible myelotoxicity. Two large studies with a prolonged duration of follow-up established a rate of myelodysplastic syndrome of approximately 2% and a rate of acute leukemia of approximately 0.5%. Advanced age, presence of bone metastases, and heavy pretreatment have been reported to increase the risk of secondary myelodysplastic syndrome, although there is some controversy as to whether prior treatment with alkylating agents, such as temozolomide, increases this risk.

The phase III NETTER-1 trial was the first prospective, randomized trial of a radiolabeled SSA. The study population consisted of patients with advanced midgut NETs, representing the most common type of well-differentiated metastatic NET. Eligible patients were required to have had baseline radiographic progression by RECIST criteria while receiving standard doses of octreotide over a period of no more than 3 years. Another key eligibility requirement was evidence of SSTR expression on all target lesions, at least as high as normal liver parenchyma (Krenning grade 2 uptake on SSTR scintigraphy). The investigational arm received 177Lu-DOTATATE administered at a fixed dose of 200 mCi intravenously every 8 weeks for four treatments followed by standard-dose octreotide. The control arm received 60 mg of high-dose octreotide LAR every 4 weeks, a treatment that was selected given the absence of any other proven second-line systemic treatments in this population. The primary endpoint was PFS by blinded central radiology review.

At the time of primary endpoint analysis, treatment with 177Lu-DOTATATE demonstrated a 79% improvement in PFS (hazard ratio [HR], 0.21; 95% CI, 0.13–0.33; p < .0001). The median duration of PFS was 8.4 months for participants in the high-dose octreotide arm and was not reached among participants in the 177Lu-DOTATATE arm. The ORR was 18% with 177Lu-DOTATATE versus 3% with high-dose octreotide, a difference that was also significant (p < .0004). Although more mature follow-up is needed to evaluate OS per the statistical plan, the interim analysis showed an HR of 0.4 for OS (p = .004, with p = .000085 as a prespecified threshold for significance). Rates of grade 3 or 4 neutropenia and thrombocytopenia were 1% and 2%, respectively. At the time of primary endpoint analysis, there was no evidence of nephrotoxicity associated with 177Lu-DOTATATE. Relatively high rates of grade 1 and grade 2 nausea and vomiting occurred in the NETTER-1 study, which were primarily attributable to the commercial amino acid formulations used for renal protection in the trial and consisted of at least 18 amino acids (as opposed to the compounded arginine/lysine formulations commonly used outside of the NETTER-1 study).

Based on the results of the NETTER-1 study as well as single-arm data submitted to regulatory authorities from the Erasmus Medical Center database, both the European Medicines Agency and the U.S. Food and Drug Administration recently approved 177Lu-DOTATATE for the treatment of advanced GEP-NETs. A standard therapeutic course consists of four cycles administered approximately 8 weeks apart. Further treatments can be administered if patients experience progression after a reasonable period of disease response or stability, typically defined as greater than 12 months. Repeat treatments often consist of two cycles each, and data indicate that salvage PRRT is a reasonable treatment option with a median time to progression of approximately 17 months. Although the maximal tolerated dose has not been clearly established, a total cumulative radiation dose of approximately 1,600 mCi (eight cycles of 200 mCi each) has been considered a reasonable lifetime limit at some institutions.

A ROLE FOR BIOMARKERS IN GUIDING NET THERAPY

Given many therapeutic advances for NETs in recent years, there have been multiple efforts to identify predictive biomarkers for select NET therapies; unfortunately, few predictive biomarkers have been clearly identified to date.

Somatostatin Analogs

As previously discussed, SSAs are often considered as initial therapy for functional symptoms as well as cytostatic control in advanced NETs; SSAs bind to SSTRs expressed on the surface of NETs. Five known subtypes of the SSTR exist (SSTR1–SSTR5); however, SSTR subtype expression for an individual NET is variable. Although the National Comprehensive Cancer Network guidelines do not limit use of octreotide LAR or lanreotide to those NETs that are SSTR positive, it was demonstrated previously that specific expression of SSTR-2 by immunohistochemistry, but not the other receptor subtypes, is associated with improved clinical outcomes (both longer PFS and OS) in metastatic NETs. It has also been demonstrated that positive SSTR-based imaging, thus confirming the presence of SSTRs on the NET cell surface,
is associated with a more favorable disease course among patients treated with SSAs.\textsuperscript{62} Thus, it is likely that SSA treatment only benefits patients whose tumors harbor the SSTR.

**Everolimus**

A role for the mTOR inhibitor everolimus in the management of well-differentiated NETs has been clearly demonstrated through the RADIANT-3 and RADIANT-4 trials.\textsuperscript{3,4} With the advances in our understanding of the molecular basis of NETs, it has been hypothesized that alterations along the mTOR pathway may enrich a patient population for everolimus. Gene and protein expression in tumor tissue specimens, circulating blood markers, as well as imaging modalities have been used to identify resistance and/or response biomarkers for everolimus; unfortunately, to date, all studies have failed to identify a NET patient cohort more likely to benefit from this targeted drug.\textsuperscript{63}

**Alkylating Agent Chemotherapy**

Evidence demonstrating a role for alkylating agents in NET management dates back several decades. It is believed that alkylating agent cytotoxicity occurs through DNA methylation at O6-guanine sites; O\textsubscript{6}-methylguanine DNA methyltransferase (MGMT) is an enzyme that maintains genomic stability, repairing these DNA changes.\textsuperscript{64,65} In glioblastoma, MGMT deficiency serves as a biomarker for response to alkylating agents.\textsuperscript{66-68} With this foundation, translational efforts to identify a predictive biomarker for alkylating agent therapy in NETs have centered on MGMT. Although early efforts suggested possible utility of MGMT assays, more recent investigations with a larger number of patients failed to show that MGMT deficiency by immunohistochemistry or promoter hypermethylation could predict response.\textsuperscript{43,47,64,69-71} With this understanding, the use of alkylating agents for disease management should not be restricted to MGMT-deficient NETs.

**PRRT**

SSTR expression on imaging studies appears to predict response to PRRT. This has been demonstrated in several studies using both baseline SSTR scintigraphy as well as \textsuperscript{68}Ga-based SSTR-PET imaging.\textsuperscript{72,73}

**SEQUENCING TREATMENT IN NETS**

The treatment strategy for patients with advanced NETs is multidisciplinary and includes systemic therapies, liver-directed treatments (i.e., bland, chemotherapy, and/or radioembolization procedures), and surgical resection. Although surgery and liver-directed therapies are important treatment modalities in NETs (particularly for liver-dominant disease), these treatment options are outside the scope of this review, which centers on systemic NET treatments.

For the treating clinician, choice of systemic therapy for NETs depends on several factors (Table 1). Specifically, as will be discussed, factors that impact drug choice include tumor functional status, avidity on SSTR imaging, tumor pathologic grade, disease bulk, and disease behavior.

### TABLE 1. Clinicopathologic-Related Factors to Be Considered for Sequencing Neuroendocrine Tumor Systemic Therapy

<table>
<thead>
<tr>
<th>Functioning tumor</th>
<th>Nonfunctioning tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSTR positive</td>
<td>SSTR negative</td>
</tr>
<tr>
<td>Low or intermediate tumor grade</td>
<td>High tumor grade</td>
</tr>
<tr>
<td>Liver-only metastases</td>
<td>Liver and extrahepatic metastases</td>
</tr>
</tbody>
</table>

Rate and pattern of tumor progression (clinical and/or radiographic) | Rate and pattern of tumor progression (clinical and/or radiographic) |

Abbreviation: SSTR, somatostatin receptor.

**Functioning Tumors**

In those NETs that are hormone secreting (i.e., functional NETs), control of symptoms from hormone secretion typically guides choice of initial therapy. Carcinoid syndrome, as a result of the release of serotonin and other vasoactive factors into the circulation, is the most frequent functional syndrome seen in approximately 20% of NETs, ranging from 8% in lung NETs to 32% in small bowel NETs.\textsuperscript{74} Functional pNETs include tumors that secrete hormones such as insulin, gastrin, glucagon, and vasoactive intestinal peptide. For patients with advanced NETs and carcinoid syndrome, SSAs are typically initiated first line and can offer control of both hormonal symptoms and tumor progression. Use of SSAs has demonstrable activity in the control of functional symptoms from NETs secreting vasoactive intestinal peptide as well as glucagon.\textsuperscript{75-77} For NETs secreting insulin and gastrin, a more limited role for SSAs has been demonstrated, because transient worsening of hypoglycemia can actually be seen in insulin-secreting NETs, and proton pump inhibitors are typically initiated in gastrin-secreting NETs to mitigate the production and release of gastric acid.\textsuperscript{26,78}

For those functional NETs initially treated with an SSA, after disease progression, future treatment decisions with regard to systemic options should take into consideration control of both hormone release as well as other tumor-specific features. Options for ongoing control of hormone release in the absence of disease progression include escalation of long-acting SSA dose, introduction of short-acting SSAs, and tumor debulking (surgical and liver-directed therapies). For patients with refractory diarrhea related to carcinoid syndrome, the novel oral serotonin inhibitor telotristat (combined with an SSA) has been demonstrated to reduce the number of daily bowel movements compared with placebo.\textsuperscript{79}

**Nonfunctioning Tumors**

For advanced, nonfunctional well-differentiated NETs, SSAs are typically initiated first line in SSTR-positive tumors, based on the results of the PROMID and CLARINET trials.\textsuperscript{7,24} However, it is important to recognize that almost all NETs included in PROMID and approximately two-thirds of NETs included in CLARINET were grade 1 with Ki-67 of less than
3%. The activity of SSAs in clinically aggressive tumors has not been well studied.

No prospective data are available to guide sequencing of therapies after progression on first-line SSA treatment. For midgut NETs, available systemic treatment options include everolimus or PRRT. The NETTER-1 study of PRRT included only patients with advanced midgut NETs who experienced progression during first-line SSA therapy. Importantly, based on this subset analysis from RADIANT-4, more than one-half of the patients included in both the everolimus and placebo arms had previously received therapy with an SSA; importantly, a benefit with everolimus was seen for all patients, with the exception of the midgut NET subgroup analysis. In RADIANT-4, the activity of SSAs in clinically aggressive tumors has not been well studied. Importantly, based on this subset analysis from RADIANT-4, as well as the prior findings from RADIANT-2, there is clear evidence that everolimus is relatively inactive in the typical, slow-growing midgut NET; thus, in this setting, if the disease is avid on SSTR imaging, PRRT would be a reasonable systemic therapy to consider prior to everolimus.

For those well-differentiated pNETs documented to be avid on SSTR imaging, SSAs again are typically initiated first line. Compared with NETs of other sites of origin, a greater number of systemic treatments are available for pNETs after progression on SSAs and include everolimus, sunitinib, cytotoxic chemotherapy, and PRRT. To date, no trial has specifically investigated sequencing of these systemic therapies. In the two regulatory phase III trials of everolimus and sunitinib in pNETs, many patients had previously received SSAs and/or chemotherapy, and no prospective investigation has been completed to date comparing chemotherapy with placebo, everolimus, or sunitinib in pNETs. Importantly, despite a lack of prospective randomized studies with chemotherapy, activity in pNETs (compared with NETs of other sites of origin) appears to be high, and chemotherapy should be strongly considered for patients with pNETs that are clinically aggressive, of high pathologic grade, and/or of high tumor burden; chemotherapy options include combination regimens incorporating either platinum or alkylating drugs, as discussed previously.

**Ongoing Studies and Future Directions of NET Clinical Research**

To date, although important strides have been made with rigorous investigation of novel systemic treatments in NETs, there remains a lack of prospective data on how to sequence these therapies. It is well recognized that future research efforts should include studies that compare the different active drugs and address the topic of sequencing, to clarify treatment paradigms for our patients. Currently, there are two ongoing multicenter clinical trials poised to address these issues for the NET patient population. SEQTOR (NCT02246127) is a prospective, randomized, open-label study to evaluate the efficacy and safety of chemotherapy (fluorouracil and streptozotocin) followed by everolimus versus everolimus followed by fluorouracil and streptozotocin in advanced and progressive pNETs. COMPETE (NCT03049189) is a prospective, randomized, open-label study to evaluate the efficacy and safety of PRRT ($^{177}$Lu-DOTATOC) versus everolimus in advanced and progressive SSTR-positive GEP-NETs. These clinical trials represent our first efforts to gain a better understanding of sequential therapy in NETs. As we look to the future, continued and ongoing clinical investigation, similar to these two prospective studies, will help elucidate how to sequence the growing number of available systemic therapies for NETs.

**References**


What Makes a Pancreatic Cancer Resectable?

Douglas B. Evans, MD

OVERVIEW

The majority of patients with localized pancreatic cancer who undergo surgery with or without adjuvant therapy will develop metastatic disease, suggesting that surgery alone is not sufficient for cure and micrometastases are present at the time of diagnosis even when not clinically apparent. As such, the field is rapidly moving to consensus on treatment sequencing, which emphasizes the early delivery of systemic therapy and the application of surgery to the population of patients most likely to receive clinical benefit from such large operations—namely, those with stable or responding disease following systemic therapy and often chemoradiation. There remains incomplete consensus about the definition of what is operable (both tumor anatomy and patient age/comorbidities) and whether the operation should be performed in a high-volume center by more experienced surgeons. In this article, we try to provide a comprehensive description of when surgery should be performed and what constitutes an operable tumor. Such information is critically important for the optimal delivery of stage-specific therapy and to allow physicians to provide accurate expectations to all patients for treatment outcome. The complex issues of where and by whom such large operations should be performed is beyond the scope of this review.

Advanced imaging technology has improved preoperative clinical staging so that “exploratory surgery” to determine resectability for known or suspected pancreatic or periampullary cancer is not necessary and should not be performed in 2018. Preoperative evaluation should include a detailed history and physical examination (including functional status), chest imaging, laboratory studies including tumor markers (CA19-9 and carcinoembryonic antigen [CEA]) at present; an expanded list of biomarkers will be available soon), contrast-enhanced pancreas-protocol CT of the abdomen, and evaluation of comorbid conditions as indicated. CT allows for assessment of the tumor’s relationship to the superior mesenteric artery (SMA), the superior mesenteric vein (SMV) and SMV–portal vein confluence (SMV-PV), the celiac artery, and the hepatic artery. CT also defines any arterial or venous aberrations (e.g., replaced left or right hepatic artery, inferior mesenteric vein draining directly into the SMV, jejunal branch of the SMV draining anterior to the SMA) and highlights potential lymph node or extra-pancreatic metastases. Clinicians can then accurately stage the patient on the basis of CT imaging: (1) resectable, (2) borderline resectable, (3) locally advanced (now to include type A and type B), and (4) metastatic (Table 1). These categories are necessary to allow for optimal multidisciplinary treatment sequencing both on and off of a clinical trial, as this article discusses.

There is an evolving recognition that pancreatic cancer is a systemic disease at the time of diagnosis, even among patients with apparent localized disease. As a result, and supported by recent data demonstrating improved overall survival for patients who are treated with multimodality therapy as compared with surgery alone, greater attention has been focused on the optimal treatment sequencing of chemotherapy, chemoradiation, and surgery for patients with localized pancreatic cancer. Inherent in the decision to deliver all three modalities (or even just chemotherapy and surgery) to a patient with localized pancreatic cancer is the accurate identification of those who have potentially operable disease at the time of diagnosis. The benefit of an objectively defined staging system for patients and physicians is obvious: the goals of therapy (to include surgery) can be specifically defined at the time of diagnosis. The goal of patients (and their treating physicians) who receive neoadjuvant treatment sequencing is eventual surgery, with the understanding of the rather modest benefit that surgery may have on disease-free survival in some patients.

As experience with preoperative staging evolved, it soon became clear that a gray zone existed between the definitions of resectable and locally advanced pancreatic cancer. Borderline resectable disease was used to define patients with arterial abutment and short SMV-PV occlusion who, in the past, would have been considered to have locally advanced disease. However, after neoadjuvant therapy, such patients with responding disease (clinical benefit, improved imaging, and a decline in tumor marker profile) were being considered for surgery—hence the development of the borderline classification. Patients with borderline resectable pancreatic cancer are different from those with resectable...
disease in that they (1) are at the highest possible risk for a positive margin of resection because of tumor-artery abutment; (2) require a more complex operation, usually involving vascular resection and reconstruction; and (3) may be at higher risk for harboring radiographically occult distant metastatic disease. For these reasons, a longer period of induction therapy, often including chemotherapy followed by chemoradiation, has been applied to this patient population. The chemoradiation portion of induction therapy is thought to be particularly important for patients with arterial abutment in the hope of sterilizing at least the periphery of the tumor and thereby preventing a positive margin of resection.

Our program, as well as national consensus guidelines, has espoused the use of objectively defined criteria for pretreatment (and preoperative/postneoadjuvant) staging (Table 1). An objective CT-based system for radiographic staging allows one to accurately identify the population of patients being treated, provides a system that may be reproducible at other institutions (necessary for the conduct of clinical trials), and allows one to define the potential for completion of all intended therapy to include surgery. In our published experience, the likelihood of successful surgery after induction therapy for patients with resectable, borderline resectable, locally advanced type A, and locally advanced type B disease are approximately 90%, 75%, 60%, and 25%, respectively (Table 2).6-9

To add clarity to the goals of treatment of patients with locally advanced pancreatic cancer, we recently described a system for categorizing this stage of disease: locally advanced type A, where surgery may be possible after systemic therapy and chemoradiation, and locally advanced type B, where surgery would likely never be possible.2 Our categories were based on a few guiding principles influenced by

### PRACTICAL APPLICATIONS

- The clinical stage of disease can be determined by accurate pretreatment CT imaging.
- The potential for an individual patient to complete all intended neoadjuvant therapy and surgery can be determined by the pretreatment stage of disease.
- Operability is objectively defined in this article, but such objectivity is based on the experience of high-volume surgical oncologists who routinely perform vascular resection and reconstruction at the time of pancreatectomy.
- Such large operations are performed only in carefully selected patients who have responded to induction therapy.
- Surgery is perhaps necessary but is rarely sufficient for the achievement of a disease-free survival of more than 2 years.

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### TABLE 1. Classification of Locally Advanced Pancreatic Adenocarcinoma Into Type A and B and Comparison With Definitions Used for Resectable and Borderline Resectable Disease

<table>
<thead>
<tr>
<th>Vascular Structures That Determine Stage of Disease for Localized Pancreatic Cancer</th>
<th>Resectable</th>
<th>Borderline Resectable</th>
<th>Locally Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor-artery anatomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA (usually pertains to tumor of head or uncinate process)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>≤ 180° (abutment)</td>
<td>&gt; 180° (encasement) but ≤ 270°</td>
</tr>
<tr>
<td>Celiac artery (usually pertains to tumor of pancreatic body)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>≤ 180° (abutment)</td>
<td>&gt; 180° (encasement) but does not extend to aorta and amenable to celiac resection (with or without reconstruction)</td>
</tr>
<tr>
<td>Hepatic artery (usually pertains to tumor of pancreatic neck/ head)</td>
<td>No radiographic evidence of abutment or encasement</td>
<td>Short-segment abutment/encasement without extension to celiac artery or hepatic artery bifurcation</td>
<td>&gt; 180° encasement with extension to celiac artery and amenable to vascular reconstruction</td>
</tr>
<tr>
<td><strong>Tumor-vein anatomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMV-PV</td>
<td>≤ 50% narrowing of SMV, PV, SMV-PV</td>
<td>&gt; 50% narrowing of SMV, PV, SMV-PV with distal and proximal target for reconstruction</td>
<td>Occlusion without obvious option for reconstruction</td>
</tr>
</tbody>
</table>

Abbreviations: PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein; SMV-PV, superior mesenteric-portal vein.

our experience. For example, one can often develop the plane of dissection between the adventitia of the artery and the surrounding autonomic perineural sheath (which may be infiltrated/inseparable from the tumor) and thereby separate the artery from the tumor. Such a dissection is usually initiated only if one does not need to cut through tumor to access the peri-adventitial plane of dissection. Therefore, 360° encasement of the SMA would require segmental resection; we are not ready to advocate for this extent of an operation for pancreatic adenocarcinoma, and therefore, complete encasement of the SMA is considered locally advanced type B. In contrast, celiac artery resection and reconstruction can be performed safely with increasing experience at high-volume centers and does not de-innervate the midgut. Therefore, complete encasement of the celiac artery is considered locally advanced type A. Our threshold for considering surgery after induction therapy is evolving, and our current thoughts on how to objectively classify the patient with locally advanced disease into categories A and B are described in Table 1.

### TABLE 2. Likelihood of Completing All Intended Neoadjuvant Therapy According to Disease Stage at Diagnosis

<table>
<thead>
<tr>
<th>Disease Stage at Diagnosis</th>
<th>Likelihood of Completing All Intended Neoadjuvant Therapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>90</td>
</tr>
<tr>
<td>Borderline resectable</td>
<td>75</td>
</tr>
<tr>
<td>Locally advanced type A</td>
<td>60</td>
</tr>
<tr>
<td>Locally advanced type B</td>
<td>25**</td>
</tr>
</tbody>
</table>

*To include successful surgery.
**Based on small numbers; a larger experience may prove this number to be overly optimistic.

**STAGE-SPECIFIC THERAPY: EVERY PATIENT NEEDS A DEFINED TREATMENT PLAN**

In light of the improved response rates seen with current systemic therapies (e.g., FOLFIRINOX [leucovorin, fluorouracil, irinotecan, and oxaliplatin], gemcitabine-nab-paclitaxel), patients who were previously thought to have nonsurgical disease are being reconsidered for surgery. Such patients have often received a lengthy course (4–6 months) of systemic therapy, frequently followed by chemoradiation, and are then found to have a good performance status with a low or normalized serum level of CA19-9. Essentially, these patients are “still standing,” and often the physician team does not know what to do with them. Such patients have clearly responded to therapy, and options may therefore include a treatment break (rarely preferred by the asymptomatic patient with a normalized CA19-9), maintenance chemotherapy (however defined), or consideration of surgery.

Surgery is often considered because there are few other attractive options, complete histologic responses are rare with systemic therapy and chemoradiation, and surgical resection of the primary tumor is thought to offer the only option for possible cure or long-term survival. It, therefore, is critically important that surgery be applied to carefully selected patients by using objective criteria and not because other therapies have been exhausted and the physician team is unsure of what to do next. Our stage-specific approach to the patient with localized pancreatic cancer can be summarized as follows.

**Resectable Primary Tumor**

We prefer neoadjuvant therapy as part of a clinical trial. Outside of a clinical trial, we are evolving to a “surgery last” or “total neoadjuvant approach” because the disease that recurs after successful surgery and is responsible for the death of the patient is usually the micrometastatic disease that exists in the liver, peritoneum, or lungs of most patients at the time of diagnosis. This fundamental reality, combined with the inability to reliably deliver adjuvant therapy after a large operation, is changing the paradigm of treatment sequencing to emphasize early systemic therapy regardless of the stage of disease. Outside of a clinical trial, for patients with resectable pancreatic cancer, we would begin systemic therapy (FOLFIRINOX or gemcitabine-nab-paclitaxel with or without cisplatin) and restage in 2 months. In the absence of disease response (change in tumor size on CT or a decline in CA19-9/CEA), we would then transition to chemoradiation. If there was a robust decline in CA19-9, an additional 2 months of systemic therapy before chemoradiation would be reasonable. For patients with an obstructed bile duct, we routinely use metal stents, which are placed before neoadjuvant therapy begins. The occasional patient who develops stent-associated acute cholecystitis is treated with a percutaneous cholecystostomy tube (not an operation), which can be removed at the time of pancreatectomy after all intended neoadjuvant therapy is completed. We continue to include chemoradiation in the multimodality treatment program for patients with operable pancreatic cancer.

It is important to note that most local recurrences develop within millimeters of the SMA and celiac artery because these vessels are immediately adjacent to a surgeon-created margin and pancreatic cancers frequently extend along the perivascular neural tissues. Although meticulous surgical technique may allow for the dissection of tumor away from the adventitia of the artery, more than 40% of patients will have residual tumor cells at the resection margin, which often remain undetected. Such patients will manifest a clinically significant local recurrence only if they escape systemic recurrence; in other words, local recurrence can occur only in living patients.

As the length of life increases as a result of more effective systemic therapy (and the reliable delivery of such therapy in a neoadjuvant fashion combined with safe surgery), more patients will be at risk for a perineural recurrence in the absence of radiation therapy to the primary tumor and associated perineural tissue and lymph nodes. At our institution, when neoadjuvant chemoradiation is delivered, the entire pancreatic head, body, or tail (depending on the site of the primary tumor) is targeted, rather than just the visible
gross tumor volume, along with the celiac artery, SMA, and SMV. This targets the perineural spread of the tumor as well as microscopic lymph nodes adjacent to the large vessels that arise from the aorta. Lesions that are near the PV, SMV-PV, inferior vena cava or aorta, or the celiac artery/common hepatic artery are also selectively targeted. Rather than comprehensively treating all regional at-risk nodal distributions, we target only suspicious regional lymph nodes. Patients are typically restaged with high-quality CT during week 4 after the completion of chemoradiation (the final part of the neoadjuvant program) and have surgery in week 5. We require patients to be free of treatment-associated toxicity (fatigue, anorexia) for a minimum of 2 weeks before operation.

Borderline Resectable Primary Tumor

Again, we prefer neoadjuvant therapy as part of a clinical trial. Outside of a clinical trial, neoadjuvant therapy is widely accepted for this stage of pancreatic cancer.12 By definition, patients with borderline resectable disease have operable tumors, but ones that require a more complex operation, and such patients are at higher risk for a positive margin of resection. As seen with resectable disease, we are evolving to a “surgery last” or “total neoadjuvant” approach because it is even more difficult to deliver adjuvant therapy to patients who have received neoadjuvant therapy and surgery (compared with surgery alone).10 Although current clinical trials are using a sandwich approach—neoadjuvant chemotherapy/surgery/adjuvant therapy—the studies to date suggest that many patients treated this way will not receive intended adjuvant therapy (for example, the ACOSOG trial presented at the ASCO Annual Meeting). Importantly, patients with borderline resectable disease have operable tumors, and therefore, a window of operability can be lost in the event of local disease progression. This is unlikely to occur after 2 months of systemic therapy but can occur after 4 or more months. Therefore, if restaging studies performed after 2 months of systemic therapy suggest the lack of response (or even subtle local disease progression), we would transition to chemoradiation.

The alternative would be to change to second-line systemic therapy, which we feel would be a mistake with this stage of disease. We have seen many patients who, at diagnosis, had borderline resectable disease and, after a lengthy course of systemic therapy (≥ 4 months), were found to have inoperable local disease. This may have been preventable with a more rapid transition to chemoradiation after 2 months of first-line systemic therapy and no obvious response (based on CT and serum biomarkers). For patients who do respond to 2 months of systemic therapy, we would continue with another 2 months, followed by restaging and then chemoradiation before final restaging and surgery.

Because pancreatic cancer is diagnosed in many patients of advanced age who may have significant medical comorbidities, there is always the concern that some patients may simply not be able to tolerate multiple treatments in series, especially to include surgery. For patients who “declare” themselves inadequate candidates for operation after the stress test of induction therapy has failed, neoadjuvant treatment sequencing was to their advantage. These patients were the ones at highest possible risk for surgical complications and the inability to recover from surgery (if done first). Even if they recovered their performance status after surgery, they would have been unlikely to receive adjuvant therapy.

Locally Advanced Primary Tumor

Again, a clinical trial is preferred. Outside of a clinical trial, neoadjuvant therapy is also widely accepted for this stage of pancreatic cancer, which was historically felt to be inoperable. The recently described categories of locally advanced disease A and B do allow the segregation of this patient population into those who are more, and less, likely to have their primary tumors surgically excised after induction therapy.3 Patients determined to have locally advanced type A disease are best treated in a manner similar to that used in patients with borderline resectable disease: In the absence of a response to 2 months of systemic therapy, we would transition to chemoradiation. In contrast, for patients with locally advanced type B tumors, we would usually change systemic therapy if a lack of response was determined (lack of clinical benefit, no change in CT or progression, and/or a lack of a significant (> 30%) biomarker decline). Because only 25% (or less) of patients with locally advanced type B tumors experience a response to induction therapy, which allows for consideration of surgery, a window of operability is not really at risk. For patients with locally advanced disease who show evidence of a response to systemic therapy (restaging at 2-month intervals), we would continue systemic therapy for 4 to 6 months and then make a final decision regarding operability. For patients who we feel can have their tumors surgically removed, we would complete neoadjuvant therapy with chemoradiation delivered with preoperative intent. For patients who are deemed unresectable, consideration should be given to definitive chemoradiation (dose escalation; dose and fractionation schedule are currently an area of intense debate and investigation). We and others have clinical trial opportunities for patients with inoperable locally advanced disease who have stable/responding disease after a minimum of 4 months of systemic therapy.

For patients who do undergo surgery, vascular resection and reconstruction add significantly to the complexity of pancreactectomy.13-15 For venous resection/reconstruction, we require a suitable proximal (PV) and distal (SMV) target for reconstruction, and we use systemic heparinization with arterial inflow occlusion on the SMA. Following venous resection, it is critically important that the SMV-PV confluence be as close to normal as possible with regard to size, shape, and contour. Whether one performs a tangential repair with saphenous vein or an interposition graft with internal jugular vein, either can look perfect or unacceptable and either can stay patent for the life of the patient or eventually occlude (resulting in extrahepatic portal hypertension and
ascites). The surgeon should not leave the operating room unless the reconstructed venous segment looks perfect because narrowing of the SMV-PV will be a problem in the postoperative period.

Pancreatic cancer involving the celiac artery often requires an Appleby procedure consisting of a distal pancreatectomy, en-bloc splenectomy, and resection of the celiac artery. However, in patients treated with neoadjuvant therapy, especially when it included chemoradiation, a plane of dissection can sometimes be developed between the adventitia of the artery and the associated nerve sheath. If the tumor/nerve sheath can sometimes be developed between the adventitia of the artery, then the common hepatic artery, left gastric artery, and celiac artery are preserved, allowing the operation to be limited to resection of the distal pancreas, spleen, involved perineurium, and lymph nodes. If the celiac artery is resected, we prefer routine reconstruction of the artery (“supercharged” Appleby) with a reversed saphenous vein graft from the proximal celiac artery to the common hepatic artery. This maneuver restores forward flow to the stomach (and liver), which may be especially important when the left gastric artery is also resected.

Pancreatic cancer that encases the SMV-PV confluence in the setting of SMA and/or celiac artery abutment/encasement represents a much more complex operative challenge (compared with just isolated celiac artery encasement) and requires a greater level of surgical experience. A temporary mesocaval shunt using a left internal jugular vein interposition graft widely opens the root of the small bowel mesentery to facilitate careful microdissection of the SMA and celiac artery, structures that are frequently within 1 or 2 cm of one another and often very hard to visualize and dissect with the SMV-PV confluence intact.

By degree of difficulty, tumors involving the pancreatic body/celiac artery are the most technically straightforward to resect and reconstruct. Those involving the pancreatic head/uncinate that require skeletonizing the root of the mesentery (SMA) as well as resection/reconstruction of the SMV are the next most challenging. Finally, tumors of the neck of the pancreas that encase both the SMV-PV and the common hepatic artery are the most technically difficult. Importantly, the degree of difficulty in performing pancreatic resection for cancer is often inversely related to tumor size; the tumors of the pancreatic neck may be the smallest, but the nuances of their surgical removal are the most complex and the most difficult.

Finally, in some centers, the use of irreversible electroporation (IRE) has been applied to patients with borderline resectable and locally advanced pancreatic cancer at the time of surgery. IRE is a nonthermal ablative technique that can be performed at the time of surgery or via a percutaneous approach. Morbidity related to IRE can be substantial, and there has been substantial discrepancy in the outcomes reported with IRE. Of note, IRE is being applied to two patient populations: those deemed unresectable, who undergo surgery just for IRE to be performed, and those whose preoperative stage is unclear, allowing the surgeon to use IRE as a plan B if the tumor is not removed or is removed with a grossly positive margin. This approach to the treatment of pancreatic cancer defies the oncologic principle of accurate preoperative staging, encourages the inappropriate use of surgery, and imparts the morbidity of a laparotomy on patients with unresectable disease who could achieve equal/superior local disease control with radiation therapy (and no operation).

Recognizing the wealth of data that support the association of higher patient volume with improved outcome, particularly with regard to pancreatic cancer surgery when vascular resection and reconstruction are required, it is inescapable that surgical expertise combined with multidisciplinary care is essential to achieve optimal oncologic outcomes. Resectability can be accurately defined on preoperative imaging, and complex vascular resection, if necessary, should be performed by surgeons experienced with venous and arterial reconstruction. Such patients should not receive IRE or any other emerging noncurative local intervention simply because the expertise does not exist to perform the required operation. We appreciate the complexity of operationalizing this recommendation at a time of increased physician employment and pressure from hospital systems to retain downstream revenue.

CONCLUSIONS

Surgery first for operable pancreatic cancer has resulted in no significant change in survival over the past 3 decades. This has been due to the inappropriate early application of a local therapy (surgery) to a systemic disease in most patients. In contrast to a surgery-first strategy, neoadjuvant treatment sequencing will ensure the receipt of systemic therapy by all patients and accurately segregate the patient population into those who will and will not benefit from surgery. With growing acceptance, neoadjuvant therapy will be the backbone for most future studies of multimodality therapy in localized pancreatic cancer. Such trials will increasingly incorporate novel investigational drug therapies and evolving techniques and fractionation schemes for the delivery of radiation therapy. Sensitive and specific diagnostic biomarkers will add to the more widespread incorporation of precise cross-sectional imaging studies, resulting in both improved disease staging and assessment of treatment response. Progress will likely continue to be measured in small advances, and our contemporary challenge will be to avail exciting clinical trials as well as state-of-the-art, off-trial therapy to all eligible patients. This will require physicians to work collaboratively across health systems at a time when hospital systems receive a significant contribution margin for the care of each patient with pancreatic cancer and “leakage” from one system to another is often actively discouraged, even for the minority of patients who may benefit from a complex surgical procedure. As physicians have become increasingly employed by multispecialty practice groups or hospital systems, keeping the patient first may pose a challenge beyond that of the low-density tumor on the CT scan.
WHAT MAKES A PANCREATIC CANCER RESECTABLE?

References


GENITOURINARY
(NONPROSTATE) CANCER
Multidisciplinary Management of Muscle-Invasive Bladder Cancer: Current Challenges and Future Directions

Jeanny B. Aragon-Ching, MD, FACP, Ryan P. Werntz, MD, Anthony L. Zietman, MD, and Gary D. Steinberg, MD

OVERVIEW

The treatment of muscle-invasive bladder cancer (MIBC) is complex and requires a multidisciplinary collaboration among surgery, radiation, and medical oncology. Although neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) and lymph node dissection has been considered the standard treatment for MIBC, many patients are unfit for surgery or cisplatin-ineligible, and considerations for bladder-preservation strategies not only are increasingly recognized as optimal treatment alternatives, but also should feature in the range of management options presented to patients at the time of diagnosis. Apart from chemotherapy, immunotherapy has also been used with success in locally advanced and metastatic bladder cancer and is moving into the MIBC space. Prospective studies addressing trends in management that span systemic, surgical, and radiation options for patients are discussed in this article.

Bladder cancer occurred in an estimated 79,030 patients in the United States in 2017 alone, with 60,490 cases occurring in men and 18,540 in women.1 The same trends were seen in Europe, with incidence rates of 19.1 per 100,000 in men and 4 per 100,000 for women.2 Although a majority are diagnosed with superficial bladder cancers,3 up to 25% present with muscle-invasive disease, for whom the risk for progression or metastasis is substantial. Prognosis and recurrences vary by stage of disease as well as other prognostic features, including lymph node involvement, lymphovascular invasion, tumor stage, presence of variant histology, and molecular subtyping.4-6 Although RC has historically been the cornerstone of treatment for MIBC, optimizing outcomes with NAC and alternative options for bladder preservation strategies have also emerged as treatment options. In this review, we discuss the multidisciplinary management of MIBC by highlighting perioperative systemic therapy, surgical management issues, and bladder-preservation techniques and principles for MIBC.

SYSTEMIC THERAPY FOR MIBC
Role of Chemotherapy in Locally Advanced Urothelial Cancer

Chemotherapy has an established role in the treatment of MIBC, either in the perioperative setting or concurrently as radiosensitizing agents with radiation. The use of neoadjuvant cisplatin-based chemotherapy was largely defined by several prospective trials that elucidated the benefit of multiagent cisplatin-based chemotherapy prior to definitive RC.7 One large prospective trial by the intergroup Southwest Oncology Group (SWOG) 8710 enrolled 317 patients and used NAC with methotrexate, vinblastine, adriamycin, and cisplatin (MVAC) followed by RC with regional lymphadenectomy (153 patients) compared with those who underwent surgery alone (154 patients).8 The combination arm was found to be associated with improved overall survival (46 months, as compared with 77 months in those who received NAC with surgery; p = .06) as well as better pathologic T0 rates in those who received NAC (38% in the NAC arm versus 15% who underwent surgery alone, p < .001). Patients who achieved a pT0 response also had a significantly higher 5-year disease-free survival at 85% compared with those with residual muscle-invasive or higher-stage disease, defining pathologic response at cystectomy as a surrogate for efficacy of NAC use. The ability to maintain dose intensity and tolerability is supported by the use of growth factors in the dose-dense or accelerated MVAC setting.9-11 The results of these smaller phase II trials are similar to the SWOG 8710 trial, where a complete response rate (pT0 at cystectomy) was seen in 15 out of 40 patients (38%; 95% CI, 23%-53%) in the accelerated MVAC setting,10 and 49% (80% CI, 38%-61%) achieved pathologic response of pT1N0M0 or lower in the dose-dense phases II setting.11 A larger phase III randomized trial that enrolled 976 patients by the Medical Research Council and the European Organization for Research and Treatment of Cancer BA06 30894...
trial evaluated the effects of NAC using cisplatin, methotrexate, and vinblastine followed by RC with lymphadenectomy or radiotherapy.\textsuperscript{17} This trial demonstrated, only upon longer follow-up after a median of 8 years, a 16\% reduction in the risk of death (hazard ratio [HR], 0.84; 95\% CI 0.72–0.99; p = .037), translating to a 6\% increase in 10-year survival from 30\% to 36\% after cisplatin, methotrexate, and vinblastine. In contrast, usual practice often dictates use of the doublet regimen gemcitabine and cisplatin (GC) given the similar efficacy but improved tolerability of GC compared with MVAC in the metastatic setting,\textsuperscript{13} with a median survival of 14 months for GC and 15.2 months for MVAC, but with lesser toxic deaths (1\% for GC and 3\% for MVAC). Frequent extrapolation in the neoadjuvant setting is seen, in which GC is used in most centers, and the pathologic complete response rates are similar (pathologic complete response for GC was 23.9\% vs. 24.5\% for MVAC; p = .2).\textsuperscript{14} However, true equivalence of the two regimens is unknown but supported by several retrospective analyses.\textsuperscript{15–18} One prospective trial led by SWOG S1314, called Co-expression Extrapolation Program to Predict Chemotherapy Response in Patients With Bladder Cancer, started enrolling patients with the goal of randomizing to either GC or dose-dense MVAC with the primary outcome of examining the relationship of dose-dense MVAC- and GC-specific Co-expression Extrapolation scores to pathologic response at cystectomy, though not specifically comparing one regimen to the other (NCT02177695). Regardless of the regimen used, the ability to achieve a complete pT0 response, which NAC would ideally strive for, serves as a surrogate for survival in several studies.\textsuperscript{19,20}

Adjuvant chemotherapy has been studied in multiple series, but it has been wrought with problems, including being underpowered in most series. More recent data\textsuperscript{21} as well as retrospective analyses have shown benefit in terms of overall and disease-free survival,\textsuperscript{22} with support for perioperative systemic therapy regardless of the sequence.\textsuperscript{23} However, one of the biggest adjuvant chemotherapy trials (the European Organisation for Research and Treatment of Cancer 30994 trial) enrolled only 284 of the planned 660 patients,\textsuperscript{24} highlighting the difficulty in accruing to these adjuvant trials. Although up-front or immediate adjuvant chemotherapy showed no improvement in overall survival compared with deferred adjuvant treatment (adjusted HR 0.78; p = .13), there was prolongation of progression-free survival with immediate compared with deferred chemotherapy (HR 0.54; p < .0001), with 5-year progression-free survival of 47.6\% in the up-front adjuvant chemotherapy group and 31.8\% in the deferred treatment group. The chemotherapy agents used were four cycles of GC, high-dose MVAC, or MVAC or six cycles of deferred chemotherapy only upon relapse. These data form the rationale of offering adjuvant chemotherapy in patients with locally advanced T3 to T4 and/or node-positive bladder cancer who have not received prior cisplatin-based NAC.\textsuperscript{25}

**Challenges of Perioperative Systemic Therapy for Locally Advanced Bladder Cancer**

Although chemotherapy has been considered the mainstay of perioperative systemic therapy, it is well recognized that not everyone will be eligible for cisplatin-based chemotherapy. In addition, slow adoption of NAC has been observed despite guideline recommendations advocating its use,\textsuperscript{26} although increasing use of NAC has been observed in more contemporary series.\textsuperscript{27} There are a lot of potential challenges to delivering cisplatin-based perioperative chemotherapy, including those considered “unfit” for cisplatin in whom cisplatin ineligibility is defined as renal insufficiency with a creatinine clearance less than 60 mL/min, hearing loss of grade 2 or more, impaired performance status with Eastern Cooperative Oncology Group performance status of 2 or higher, neuropathy of grade 2 or higher, and cardiac dysfunction as defined by New York Heart Association class III heart failure.\textsuperscript{28} Substitution with carboplatin has demonstrated suboptimal responses in the metastatic setting.\textsuperscript{29} Thus, patients who are considered unfit or ineligible for cisplatin should therefore be considered for up-front surgery given the concern for delay of definitive treatment that may compromise outcomes. Although age is not necessarily a factor that precludes cisplatin eligibility, most patients with bladder cancer do have advanced age at presentation, and studies have shown that creatinine clearance of less than 60 mL/min, a common criterion for cisplatin eligibility, is more prevalent with older age.\textsuperscript{30} In contrast, efforts to improve response rates with varying combinations and other targets have been attempted. Similarly, alternative agents (other than cisplatin), such as low-dose gemcitabine or 5-fluorouracil/mitomycin, have been used concurrently with radiation, though mostly as radiosensitizing agents, and will be discussed further in the bladder-preservation strategies below.

**Use of Checkpoint Inhibitors/Targeted Agents and Biomarkers of Response**

Given the striking benefit of the use of checkpoint inhibitors in patients with unresectable and metastatic bladder cancer in the salvage second-line setting in whom five PD-1/PD-L1 drugs are currently approved,\textsuperscript{31} efforts to examine the utility of PD-1/PD-L1 inhibitors in the first-line treatment of patients who are ineligible for cisplatin has led to the U.S. Food

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**PRACTICAL APPLICATIONS**

- Neoadjuvant cisplatin-based chemotherapy remains the standard systemic therapy for cisplatin-eligible patients undergoing RC and lymphadenectomy.
- Maximal TURBT followed by chemoradiation is an alternative option for patients who refuse cystectomy or otherwise choose bladder-preservation techniques.
- Increasing knowledge regarding biomarkers of response to chemotherapy, radiation, or cystectomy may pave the way for selecting patients for different modalities.
- Multidisciplinary collaboration between surgery, radiation oncology, and medical oncology brings about the best outcomes for MIBC.
and Drug Administration approval of atezolizumab and pembrolizumab for the first-line therapy of locally advanced and metastatic bladder cancer.32,33 Efforts to extrapolate these results in the neoadjuvant (Table 1) and adjuvant settings are also underway with a multitude of trials. For instance, in patients with muscle-invasive or node-positive urothelial cancer who have undergone surgery, there are currently several adjuvant immunotherapy trials, including use of atezolizumab compared with observation (IMVigor010 trial; NCT02450331), nivolumab compared with placebo (CheckMate 274; NCT02632409), and pembrolizumab compared with placebo (AMBASSADOR, sponsored through Alliance for Clinical Trials in Oncology, A031501; NCT03244384). Data were gleaned from the initial Cancer Genome Atlas (TCGA) analyses, as the updated report showed compelling therapeutic targets that can be exploited with five different subtypes stratified into luminal, luminal-papillary, luminal-infiltrated, basal, and neuronal.34 The use of other targets such as VEGF inhibitors is promising in the second-line salvage setting, such as ramucirumab35,36 and fibroblast growth factor receptor inhibitors. There are other evolving immune targets that serve to bypass resistance to immunotherapy in the advanced/metastatic setting, such as the use of IDO inhibitors, adenosine-A2A receptor small-molecule inhibitors, dual costimulatory targeting ofOX-40 and 4-1bb, monoclonal antibody to B7H3, and the use of an antibody-drug conjugate composed of an anti–nectin-4 monoclonal antibody attached to monomethyl auristatin E, called enfortumab vedotin (ASG-22ME), with promising trials all underway,37 though it remains to be seen if these targeted agents would be tested in the neoadjuvant setting. A study looking at the combination of ramucirumab and pembrolizumab in a phase I study for patients with urothelial carcinoma with documented disease progression after one to three prior lines of systemic therapy is underway (NCT02443324). Other potential targets, such as erlotinib, are being examined in the neoadjuvant setting (NCT02169284). However, combinations that include GC chemotherapy with VEGF inhibitors such as sunitinib resulted in excess toxicity.38 The use of neoadjuvant MVAC with bevacizumab in conjunction with gene expression profiling showed that the addition of the VEGF-targeted agent probably yielded no additional benefit, although the segregation into different subtypes of basal, p53–like, and luminal showed that the basal type was most predictive of response and survival to chemotherapy.39 Tumors with p53 subtypes consistently show chemoresistance.40 A genomic-based biomarker validation study showed that patients whose tumors express genomic alterations in the DNA repair genes such as ATM, RB1, and FANCC were more likely to have improved pathologic response (p < .001; 87% sensitivity, 100% specificity) and better overall survival (p = .007) to cisplatin-based NAC.41 However, these findings may not necessarily predict exclusive responses to chemotherapy and may indicate response to immunotherapy as well. In addition, these data are too preliminary to start applying TCGA subtypes to decide who should receive NAC in practice. Increased PD-L1 expression was predictive of response in the advanced immunotherapy trials,42 although lack of expression does not necessarily preclude usefulness because responses, albeit lower, are still seen in those with lower marker expression. Strategies to combine chemotherapy with immunotherapy are underway.43 The inclusion of immunotherapy in the treatment paradigm of MIBC as neoadjuvant, adjuvant, or concurrent with bladder preservation is the subject of ongoing clinical investigation (Table 1).

**SURGICAL MANAGEMENT OF MIBC**

**High-Quality Transurethral Resection of Bladder Tumor**

Bladder cancer diagnosis and management begins with a high-quality transurethral resection of bladder tumor (TURBT). Inadequate resection can lead to considerable understaging and misdiagnosis, with patients receiving intravesical therapy for presumed non-MIBC when in fact they have muscle-invasive disease. Despite recently updated American Urological Association and European Association of Urology guidelines that strongly recommend repeat TURBT in patients with high-grade T1 or high-volume, high-grade Ta, complete transurethral resection remains challenging.44 When performing a repeat TURBT, approximately 70% of patients will have remaining visible tumors, with the majority away from the resection site. These findings have been attributed to lack of detection of tumors using standard white-light cystoscopy. More recently, blue-light cystoscopy (BLC) is being used in the initial diagnosis and staging of bladder cancer. Photodynamic diagnosis uses the photodynamic properties of hexamethineolevulinate (HAL). Following intravesical installation, the HAL binds to protoporphyrin IX, which preferentially accumulates in neoplastic cells. The blue light causes the HAL bound to protoporphyrin IX to fluoresce red. The use of BLC with HAL has shown clinical benefit in five prospective international clinical studies involving more than 1,800 patients. The main benefit is seen in the detection of carcinoma in situ, where BLC compared with white-light cystoscopy detected around 40% (odds ratio, 12.3) more cases and at least one additional papillary tumor in 25% of cases.45 The use of BLC cystoscopy has been associated with an increase in the detection of tumors and reduction in the recurrence rate, but has questionable impact on progression rates.46,47 With the improvement in staging with BLC, the hope is to more accurately diagnose patients and provide the optimal treatment regimen.

**Radical Cystectomy**

Once the diagnosis of MIBC is made, management must be optimized because the risk of morbidity and mortality is noteworthy. Currently in the United States, after considering NAC, the gold-standard treatment is RC and urinary diversion. RC alone may cure the majority of patients with pathologically organ-confined pT2 disease, approximately 50% to 60% of patients with pT3 disease, and 20% to 30% of patients with pT4 of low-volume lymph node–positive pN1

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<table>
<thead>
<tr>
<th>Trial Name</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Patient Population</th>
<th>Phase of Trial</th>
<th>Arms of Trial</th>
<th>Primary Objective</th>
<th>Secondary Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant Pembrolizumab in Combination With Gemcitabine Therapy in Cis-eligible/Ineligible UC Subjects</td>
<td>NCT02365766</td>
<td>Clinical stage cT2-4aN0M0</td>
<td>Phase 1B/II</td>
<td>Dose-finding cohort: pembrolizumab at starting dose of 200 mg (dose level 0), and/or 120 mg (dose level -1) in combination with gemcitabine and cisplatin.</td>
<td>Phase 1B: safety and tolerability; phase II: rate of pathologic response</td>
<td>Relapse-free survival, overall survival</td>
</tr>
<tr>
<td>Multi-Institutional Phase II Study of Radiation Therapy and Anti–PD-L1 Checkpoint Inhibition (Durvalumab) With or Without Anti–CTLA-4 Inhibition (Tremelimumab) in Patients With Unresectable, Muscle-Invasive or Metastatic Urothelial Bladder Cancer That Are Ineligible or Refusing Chemotherapy</td>
<td>NCT03150836</td>
<td>Locally advanced (cT3 or cT4) or metastatic (N+ or M+) urothelial bladder cancer; mixed histologies with predominant urothelial pattern are allowed</td>
<td>Phase II</td>
<td>Regimen A: durvalumab + RT; regimen B: durvalumab + tremelimumab + RT</td>
<td>Toxicity according to NCI CTCAE v. 4.03 criteria; progression-free survival</td>
<td>Pathologic complete response, local control, overall response rate, overall survival</td>
</tr>
<tr>
<td>Pembrolizumab (MK3475), Gemcitabine, and Concurrent Hypofractionated Radiation Therapy for Muscle-Invasive Urothelial Cancer of the Bladder</td>
<td>NCT02621151</td>
<td>Clinical stage T2–T4aN0M0</td>
<td>Open-label phase II</td>
<td>Pembrolizumab 200 mg IV every 3 weeks starting D1 of RT; gemcitabine 27 mg/m² twice weekly for 4 weeks during RT; EBRT x 52 Gy x 20 fractions</td>
<td>2-year bladder-intact disease-free survival rate</td>
<td>Safety, complete response, overall survival</td>
</tr>
<tr>
<td>Phase 1B Study to Assess Safety and Efficacy of Neo-Adjuvant Bladder Urothelial Carcinoma Combination-immunotherapy (NABUCCO)</td>
<td>NCT03387761</td>
<td>cT3-4aN0 or T1, cN+, or T1, any N, resectable retroperitoneal lymph node metastasis; cisplatin-ineligible or refusal</td>
<td>Phase 18 single-arm open-label</td>
<td>Day 1: ipilimumab 3 mg/kg IV; day 22: ipilimumab 3 mg/kg + nivolumab 1 mg/kg IV; day 43: nivolumab 3 mg/kg IV</td>
<td>Safety</td>
<td>Efficacy, resistance mechanisms</td>
</tr>
<tr>
<td>Pre-Surgical Study Evaluating Anti–PD-L1 Antibody (Durvalumab) Plus Anti–CTLA-4 (Tremelimumab) in Patients With Muscle-Invasive, High-Risk Urothelial Carcinoma Who Are Ineligible for Cisplatin-Based Neoadjuvant Chemotherapy</td>
<td>NCT02657486</td>
<td>ct2–3aN0M0; cisplatin-ineligible or refusal</td>
<td>Pilot study</td>
<td>Durvalumab and tremelimumab by vein on day 1 of weeks 1 and 5</td>
<td>Safety</td>
<td>Immune and molecular changes</td>
</tr>
<tr>
<td>A Phase II Study Evaluating Neoadjuvant Pembrolizumab Monotherapy in Patients With Muscle-Invasive Bladder Cancer to Explore In Vivo the Mechanisms of Action of Pembrolizumab</td>
<td>NCT03212651</td>
<td>ct2–T4aN0/XM; cisplatin-ineligible or refusal</td>
<td>Open-label phase II</td>
<td>Pembrolizumab 200 mg IV every 3 weeks for three cycles prior to cystectomy</td>
<td>Pathologic complete response</td>
<td>None listed</td>
</tr>
<tr>
<td>Neoadjuvant Nivolumab With and Without Urelumab in Patients With Cisplatin-Ineligible Muscle-Invasive Urothelial Carcinoma of the Bladder</td>
<td>NCT02845323</td>
<td>cT2–T4N0-1M0; cisplatin-ineligible or refusal</td>
<td>Randomized phase II</td>
<td>Arm A, nivolumab in combination with urelumab or arm B, nivolumab monotherapy</td>
<td>Immune response to treatment as measured by tumor-infiltrating CD8+ T-cell density at cystectomy</td>
<td>Treatment-related adverse events; pathologic response; prognostic value of tumor biopsy</td>
</tr>
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(Continued)
D1, Day 1; EBRT, external beam radiation therapy; D8, Day 8.

Accurate staging and prognosis.

A thorough pelvic lymph node dissection is paramount for fit, but this is beyond the scope of this article.49 RC in men or timely cystectomy may offer the greatest survival benefit.48 In patients with high-risk non-MIBC (i.e., cT1 with lymphovascular invasion or cT1 with carcinoma in situ), early or timely cystectomy may offer the greatest survival benefit, but this is beyond the scope of this article.49 RC in men involves removal of the bladder, prostate, seminal vesicles, and pelvic lymph nodes. In women, RC involves anterior pelvis exenteration (i.e., removal of the bladder, urethra, uterus, ovaries, fallopian tubes, anterior wall of the vagina, and pelvic lymph nodes). Organ-sparing RC in female patients, defined as sparing the vagina and uterus or preservation of the neurovascular tissue along the antero-lateral vaginal wall that may improve sexual and voiding mechanics,50 has been gaining more widespread acceptance in patients who choose an orthotopic neobladder.51 Patients who have clinical evidence of a cT3 tumor (i.e., hydronephrosis or palpable mass on examination) or who have a posteriorly located tumor along the trigone are not ideal candidates for organ preservation.52 In properly selected patients, the risk of local recurrence after RC is low. In the largest series of 30 consecutive female patients with clinical T2a to T3b tumors, only one patient experienced a local recurrence with a median follow-up of 35.7 months.53 In addition to a high-quality RC, a thorough pelvic lymph node dissection is paramount for accurate staging and prognosis.

Lymph Node Dissection

Standard pelvic lymph node dissection includes the proximal boundary of the bifurcation of the external and internal iliac vessels, distally the circumflex iliac vein, laterally the genitofemoral nerve, and deep the obturator fossa and presacral nodes. An extended node dissection is along the common iliac vessels to the bifurcation of the aorta with some surgeons advocating a supraextended dissection up to the inferior mesenteric artery. These extended dissections may be reasonable and supported by retrospective data that suggest a therapeutic benefit from the extent of lymph node dissection.54 It is rare to have skip lymph nodes metastases (i.e., negative lymph nodes in the standard portion of the dissection but positive in the extended portion alone).55-57 It is likely that some of the survival benefit findings may be due to the “Will Rogers phenomenon,” in which more accurate staging leads to the conclusion for a therapeutic benefit from the extended node dissections. Two randomized clinical trials are attempting to determine the therapeutic role of extended compared with standard lymph node dissection in MIBC. The SWOG 1011 trial is currently still in accrual. The preliminary results of the European trial, which randomly assigned 183 patients to an extended and 190 patients to a limited lymph node dissection, found no difference in recurrence-free survival (69% vs. 62%; p < .01).58 On the post hoc analysis, there was an improvement in 5-year recurrence-free survival in patients with pT2 disease only (85% vs. 62.5%; p < .01). One possible reason for the lack of difference seen in their primary endpoint (recurrence-free survival) was that median nodal count of 19 in the limited cohort might have been more extensive than a true limited pelvic lymph node dissection. Hopefully, the results of SWOG 1011 will help clarify the therapeutic value of an extended lymph node dissection in bladder cancer. Although there are no clear data regarding improved survival with an extended lymph node dissection, is staging improved by an extended node dissection? In a study in which patients are found to have positive lymph nodes, up to 34% of the patients had positive nodes above the aortic bifurcation and presacral areas, outside the standard pelvic lymph node dissection template.59 However, all of these patients had pelvic lymph node metastasis. The concept of skip lesions has only been reported in one patient.60 Another study examined the impact of an extended node dissection, in which node packets were sent from each zone, and determined that a standard

### TABLE 1. Select Ongoing Neoadjuvant and Concurrent Radiation Trials Using Checkpoint Inhibitors for MIBC (Cont’d)

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Patient Population</th>
<th>Phase of Trial</th>
<th>Arms of Trial</th>
<th>Primary Objective</th>
<th>Secondary Objective</th>
</tr>
</thead>
<tbody>
<tr>
<td>An Open-Label, Single-Arm, Phase 2 Study of Neoadjuvant Pembrolizumab (MK-3475) Before Cystectomy for Patients With Muscle-Invasive Urothelial Bladder Cancer</td>
<td>NCT02736266</td>
<td>T2–T4aN0M0 MIBC</td>
<td>Open-label phase II</td>
<td>Pembrolizumab 200 mg IV every 3 weeks for three cycles prior to cystectomy</td>
<td>Pathologic complete response</td>
<td>Adverse events</td>
</tr>
<tr>
<td>Phase II Single-Arm Study of Gemcitabine and Cisplatin Plus Pembrolizumab as Neoadjuvant Therapy Prior to Radical Cystectomy in Patients With Muscle-Invasive Bladder Cancer</td>
<td>NCT02690558</td>
<td>T2–T4a N0/X M0</td>
<td>Open-label phase II</td>
<td>Pembrolizumab 200 mg IV every 3 weeks + gemcitabine 1,000 mg/m² D1 and D8 + cisplatin 70 mg/m² D1 every 3 weeks for four cycles prior to cystectomy</td>
<td>Pathologic downstaging to &lt; pT2 after neoadjuvant therapy</td>
<td>Event-free survival, overall survival</td>
</tr>
</tbody>
</table>

Abbreviations: MIBC, muscle-invasive bladder cancer; UC, urothelial carcinoma; RT, radiation therapy; NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events; IV, intravenously; D1, Day 1; EBRT, external beam radiation therapy; D8, Day 8.
pelvic lymph node dissection correctly identified nodal metastasis in 100% of patients. However, if limited to a standard template, 43% of patients would have had nodal disease left in situ. They hypothesize that removing the additional positive lymph nodes may have a therapeutic benefit, but this is not supported by their data.61 Currently, the therapeutic value of an extended pelvic lymph node dissection up to the aortic bifurcation or inferior mesenteric artery is unknown, and a standard lymph node dissection is sufficient to provide accurate staging information. Performing an extended node dissection will result in more operative time and can contribute to more complications with unknown clinical benefit.

Surgical Volume

RC is a procedure associated with considerable morbidity. In a study at Memorial Sloan Kettering Cancer Center, the morbidity and mortality results were reported on 1,142 consecutive patients receiving RC. They found that 64% of patients had a complication in the first 90 days, 13% being major complications. Their 30-day mortality rate was 1.5%.62 These data highlight that even patients treated at very high-volume centers have substantial complications. A study examining surgeon volume and operative mortality in the United States using national Medicare claims found that surgeon volume was inversely related to operative mortality in all eight index procedures examined.62 The adjusted odds ratio for operative death for RC was 1.83. Surgeon volume had a greater impact on outcomes in RC when compared with a lung resection for cancer, abdominal aortic aneurysm repair, aortic valve replacement, carotid endarterectomy, and coronary artery bypass. Together, these data highlight the importance of the hospital setting with high-volume experience treating high-acuity, complex, surgical patients but also high-volume RC.

Urinary Reconstruction

Although RC is complex and drives the oncologic outcomes in bladder cancer, many of the complications arise from the urinary diversion. When it comes to urinary diversions, patients have a number of options from which to choose. Patients who elect to undergo an orthotopic urinary diversion or a continent catheterizable pouch often require more follow-up and may have higher complication rates when compared with ileal conduits.53 For the properly selected patient, however, continent diversions may be an excellent option potentially providing more natural urinary function, body image, and sociability. Quality of life assessments have been performed by multiple institutions in an attempt to answer which diversion is associated with the best quality of life. The results have been mixed. Each diversion is associated with advantages and disadvantages, and patients must be counseled to make an informed decision that best suits their needs.64

Complications

RC with diversion is associated with many different types of complications. Common complications include ileus, small bowel obstruction, urinary tract infections, fluid collections, lymphoceles, and thromboembolic events. Strategies have been used in an effort to reduce the length of stay and readmission rates. Alvimopan, a peripherally acting opioid receptor antagonist, was shown to significantly reduce the length of stay, time to gastrointestinal recovery, and postoperative ileus in a multicenter, randomized, double-blind, placebo-controlled trial for patients undergoing RC.65 This medication, along with no mechanical bowel preparation, has been implemented in enhanced recovery pathways across the world in an effort to improve postoperative care in patients with RC. Venous thromboembolism remains a considerable concern in radical pelvic surgery, in which events can be as high as 10% to 15%. It has been our practice that all patients who undergo RC are discharged home with a 30-day course of enoxaparin. This is because many of these thromboembolic events occur when the patients leave the hospital.66,67 One of the more common and difficult to manage complications is the ureteral anastomotic stricture.

In most series, the ureteral anastomotic stricture rate is somewhere between 3% and 10%, with most (70%) being left-sided ureteral strictures.68,69 Many efforts have been made to minimize the stricture rate by preserving as much periureteral tissue as possible and performing an interrupted anastomosis. In a large retrospective series, the ureteral stricture rate was evaluated with 149 and 109 consecutive patients with an interrupted and a running anastomosis, respectively. The stricture rate per ureter was 8.5% in the interrupted group and 12.7% in the running group. On multivariable analysis, a running anastomosis was associated with a higher stricture rate in this study, this was not a randomized trial, and the most important factor is thought to be a robust blood supply. The left ureter is extensively mobilized and often devascularized, likely contributing to the observed higher left ureteral stricture rate. A recent study attempted to create a diversion using a porcine model to reduce the left ureteral stricture rate by anastomosing the ureter in situ on the left side without bringing it under the sigmoid mesentery. The proposed orthotopic diversion uses two afferent limbs in a simple U-pouch configuration without compromising on compliance or capacity. This has not been validated clinically but may aid in reducing the ureteral stricture rate.70

Robotic Versus Open Cystectomy

Robotic-assisted cystectomy is becoming more common in the United States, where roughly 25% of RC are now being performed robotically.72 Recently, a randomized trial comparing robotic compared with open RC was completed.73 However, all of the urinary diversions performed were open. One of the main critiques of the robotic technique is the quality of the lymph node dissection. The trial randomly assigned 60 patients to robotic RC and 58 to open RC. There was no difference in 90-day complication rates, hospital stay, and pathologic outcomes, including lymph node count. The robotic approach was associated with a lower blood loss
(p < .02) but significantly longer operative times. The initial concerns about margin status and inadequate lymph node dissection with robotic cystectomy were associated with the learning curve, and likely these procedures are oncologically equivalent. However, it is important to note that robotic cystectomy has not shown a benefit in terms of length of stay, oncologic outcomes, or lymph node yield. There are some concerns that robotic cystectomy or the pneumoperitoneum associated with robotic surgery may alter the recurrence rates in bladder cancer after RC. In a recent publication, robotic cystectomy was associated with higher rates of peritoneal carcinomatosis (21% [9 out of 43] vs. 8% [2 out of 26]) and extrapelvic recurrences when compared with open RC.74 This highlights the importance of further investigation into robotic surgery for MIBC. The higher cost associated with robotic RC has been well documented and must be weighed when considering using this technology in the treatment of MIBC without any notable clinical benefit.75,76

CONTEMPORARY BLADDER-SPARING MANAGEMENT OF MIBC

Across the field of oncology organ preservation, a combination of debulking surgery, radiation, and systemic therapy has become a standard of care. The most well-recognized and deeply established examples are seen in breast, head, neck, and anal cancers, although many other examples exist. Although RC is still considered the gold standard for MIBC treatment in the United States, this is not uniformly the case around the world. In the United Kingdom, 60% are managed primarily with organ-preserving strategies, with cystectomy reserved for salvage.

The basic principles of organ conservation are that (1) the organ can be preserved in a functional state and with little residual impacting on quality of life, (2) the organ-preserving strategy does not preclude salvage surgery, and (3) overall survival is not compromised by an attempt at initial organ preservation.

If these goals can be achieved, then organ-preserving strategies should feature in the range of management options presented to patients at the time of diagnosis.

TREATMENT ALGORITHM FOR BLADDER-SPARING THERAPY

The current state of organ preservation in MIBC is the cumulative result of thousands of patients being entered into prospective studies in Europe, Canada, and the United States over the last 30 years.77-86 Although strategies may differ from nation to nation in detail, they do not differ in principle, which includes the following:

- Selection of appropriate cases
- Initial high-quality maximal TURBT
- External beam radiation therapy with concurrent sensitizing chemotherapy
- Cystoscopic assessment of treatment response with prompt cystectomy for nonresponders
- Regular, subsequent, cystoscopic surveillance with a cystectomy at the first sign of invasive recurrence

Case Selection

Patients with cT2 and T3a tumors, those with tumors less than 5 cm, and those with unifocal disease are those for whom good local control can be anticipated. In part, this is because they can be readily debulked. Multivariable analyses have shown that large multifocal tumors and those with tumor-related hydronephrosis have lower rates of local control.78,85 These patients may be better served by RC, assuming there is no evidence of distant metastases. Most invasive tumors are high grade, and grade does not feature into selection. Recent studies have suggested that the histologic variants, such as micropapillary disease, do not fare any worse with chemoradiation than pure urothelial cancers and thus may also be treated with chemoradiation.87 However, it goes without saying that a poorly functioning bladder as a result of extensive Tcis or much prior treatment with intravesical therapy will only function worse after chemoradiation. Therefore, such patients may be better directed toward radical surgery and reconstruction.

Debulking Surgery

Achievement of high-quality and maximal TURBT cannot be overstated. Although a biopsy is necessary to establish the diagnosis prior to RC, a visibly complete resection should be attempted and achieved prior to chemoradiation. Although it is well recognized that a small proportion of patients can be cured by TURBT alone, this is not the case for most patients. Aggressive TURBT appears to improve the rates of local control by chemoradiation by as much as 20%.85

Chemoradiation

Radiation is given at doses of 55 to 65 Gy, substantially lower than those used in prostate cancer, because urothelial cancers are substantially more radiosensitive. If radiation is used alone, long-term local control rates of around 30% to 40% have historically been reported. In the United States, a series of trials by the Radiation Therapy Oncology Group (RTOG) has explored different forms of radiation (once a day or twice a day), NAC, and concurrent sensitizing chemotherapy.78,80,82-84 NAC has not been shown to be of additional value with radiation, unlike in conjuction with surgery, and therefore does not feature in current protocols. Concurrent chemotherapy, however, adds substantially to local control. In the United States, the most favored regimen on cooperative protocols has been twice-daily radiation together with concurrent cisplatin and 5-fluorouracil. In the United Kingdom and at the University of Michigan, gemcitabine has been used as an alternative radiosensitizer together with once-daily radiation.86 RTOG 0712, a randomized phase II comparison, suggests that these regimens are equivalent and that the gemcitabine carries less toxicity.84 This may prove to be the arm that will be carried forward into future studies. Mitomycin-C and 5-fluorouracil, drugs that are routinely used to effectively radiosensitize anal cancers, have been tested in a large British randomized trial in MIBC.81 However, this trial used radiation alone as the comparator arm, not an alternative chemotherapy regimen. This
combination also yielded local control rates of over 70%. The choice of chemotherapy may then depend upon the age of the patient, the presence or absence of renal, hearing, or neurologic baseline problems or other cisplatin-eligibility criteria, and on local geographic preference. When patients are selected for organ preservation and managed with TURBT and chemoradiation, local control rates in excess of 80% are now being regularly reported.

**Prompt Salvage of Local Failures**

In the United States, cystoscopy is performed at a mid-point during the radiation (usually around 40 Gy) and salvage cystectomy recommended in the case of incomplete responses. This has the advantage of directing the patient to surgery before receiving full radiation doses. It has the disadvantage of occasionally recommending cystectomy to patients who were on their way to a complete response but simply had not gotten there yet. Following completion of full-dose chemoradiation, a cystoscopy every 3 to 6 months is recommended. Approximately 20% of those who achieve a complete response will have a subsequent superficial relapse (Ta, T1, and T1c1), and about 15% will have a future invasive relapse. It is the latter that needs cystectomy. The prompt employment of salvage cystectomy is probably one of the reasons why, in the many attempts made to compare disease-free survival outcomes, those receiving initial organ preservation seems to be indistinguishable from those who had an immediate initial cystectomy. The complication rate after salvage cystectomy is only very modestly higher than that seen after an initial cystectomy. A patient choosing to take the path of organ preservation may, however, have lost the chance to be reconstructed with an orthotopic neo-bladder because of vascular changes and fibrosis within the pelvis.

In the absence of randomized trials, many attempts have been made to compare survival outcomes after cystectomy or bladder-preserving strategies. However, difficulties in matching arise between the use of clinical and pathologic staging systems, but when sophisticated attempts are made to address and balance these issues, then, stage for stage, survival appears to be close, if not the same. Given the lack of randomized trials that have been successfully completed, these are likely to be the best data available for a long time.

**Quality of Life**

Investigators from Boston reported a study on patients receiving TURBT, chemotherapy, and radiation in the treatment of the bladder cancers with a median time from the treatment of over 6 years, sufficient to capture the majority of the late radiation side effects. Seventy-five percent of patients had normal functioning bladders by urodynamic study, with reduced bladder compliance seen in 22% of patients. Quality of life questionnaires using recognized instruments showed bladder symptoms to be uncommon, particularly in men. Bowel symptoms were, however, more common, occurring in 22% of patients and causing distress in 14%. This small but detectable level of lasting bowel distress could be considered the additional price that these patients paid to retain their bladders.

A more recent cross-sectional questionnaire study attempted to compare the quality of life of cystectomy with chemoradiation in a similar population with long follow-up. Using six different validated quality of life instruments and propensity score matching, multivariable analysis demonstrated better general quality of life in those who received chemoradiation when compared with RC. It was also associated with superior physical, social, emotional, and cognitive functioning as well as better functioning in the bowel and sexual domains.

**Biomarkers**

In an ideal world, biomarkers would be used to refine the selection of patients for chemoradiation. In exploratory studies conducted by RTOG, altered expression of p53, CDKN2A, and pRB had no prognostic significance, but overexpression of HER2 was correlated with a reduced complete response rate. This has led to a feasibility trial in which trastuzumab was combined with chemoradiation for those patients who overexpress HER2. In the United Kingdom, MRE11 is being studied for potential predictive value for radiation-treated patients. It is one of many DNA damage-signaling proteins active in the process of DNA double-strand break repair. Standardizing the assessment of MRE11 expression is proving difficult, and this marker is yet to be validated in other series. As mentioned earlier, given increased PD-L1 expression as predictive of response, there are now plans afoot by the cooperative groups to test this and other PD-L1 inhibitors as a component of organ-preserving strategies for MIBC.

**CONCLUSION**

The treatment of MIBC is complex and requires a multidisciplinary collaboration among surgery, radiation, and medical oncology. Although perioperative chemotherapy followed by RC and pelvic lymph node dissection has been established as a standard treatment of MIBC, many patients are either unfit for surgery or ineligible for cisplatin; thus, bladder preservation employing the combination of maximal TURBT, sensitizing chemotherapy, and radiation is now an established part of the therapeutic landscape in MIBC. The bladder cancer guidelines published by the American Urological Association, ASCO, the American Society for Radiation Oncology, and the Society of Urologic Oncology now incorporate the selective use of these strategies. It may be the preferred management in elderly patients, those with too many other comorbid conditions to consider cystectomy, and in those who, after a good discussion of the alternatives, simply choose it. In the past couple of years, there has been a rapid evolution in bladder cancer treatment with immuno-oncology, especially checkpoint inhibitors as single agents and/or in combination therapy in the first- and second-line metastatic bladder cancer settings. The multidisciplinary treatment of patients with MIBC offers the best approach and yields the best outcomes for such patients.
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State-of-the-Art Management of Germ Cell Tumors

Darren R. Feldman, MD

OVERVIEW

The state of the art management of germ cell tumors (GCT) in 2018 does not include novel agents targeting genomic alterations or exciting immunologic-based approaches but rather the avoidance of pitfalls in everyday practice. The relative rarity of GCT and high curability with correct management create the "perfect storm" for high-stakes errors to occur. This review focuses on several common pitfalls that should be avoided in staging and management of early-stage and advanced GCT in order to maximize patient outcomes. A particularly frequent misstep is to base treatment decisions on pre- rather than postorchectomy tumor markers that, depending on marker directionality, can lead to either undertreatment with potentially inferior outcomes or overtreatment with excess toxicity. Another common mistake is the failure to consider the unique ability of GCT to differentiate and the distinct biology of teratoma (chemoresistance and lack of increased glucose uptake compared with normal tissue), which exerts a pervasive influence on nonseminoma management. This may lead to inappropriate use of PET scan to evaluate the postchemotherapy residual mass and, if negative, the conclusion that surgery is not needed whereas (FDG-negative) teratoma should be removed. It could also result in administration of additional unnecessary chemotherapy to patients with marker normalization but without robust radiographic response after 3 to 4 cycles of BEP. Finally, oncologists should strive to maintain standard chemotherapy doses, not substitute carboplatin for cisplatin, and refer to expert centers when expertise (e.g., RPLND) is not available locally in order to achieve optimal cure rates in advanced disease.

A review of the state of the art in managing germ cell tumors (GCTs) in 2018 differs from that of virtually all other malignancies in which novel therapies releasing checkpoints in the immune system or targeting a mutation integral to the biology of the tumor are leading to unparalleled dramatic improvements in outcome with minute-to-minute change in the standard of care. Nevertheless, GCT enthusiasts can take solace in the fact that despite all of the progress being made in these other malignancies, sensitivity to available therapy and cure rates remain higher in the setting of metastatic GCTs than any other cancer, particularly if treatment is correctly applied. The truth is that in GCTs, there has not been as much of a change in treatment options as there has been reinforcement of the knowledge already learned and putting that knowledge into practice in the management of the disease.

Despite a lack of new options for managing GCTs, the rarity of the tumor and multifaceted treatment continue to present difficult challenges for the busy oncologist and urologist. There are several nuances that are not easily acquired by treatment of one or two cases per year, and robust surgical experience with GCTs, particularly performance of retroperitoneal lymph node dissections, is limited to only a few centers in each country. Both historic and contemporary data indicate that patients treated at high-volume centers achieve superior outcomes to those treated in the community. The following review will focus on the most common pitfalls being made in clinical practice that prevent state-of-the-art management (Table 1).

DIAGNOSIS AND STAGING

A frequent mistake made during the staging of newly diagnosed GCTs is the inability to resist using newer but unnecessary imaging technologies in disease assessment. PET scanning, although useful in staging many malignancies, has essentially no role in the diagnosis or staging of GCTs, even in seminoma. Results may lead to identification of clinically insignificant findings, causing increased patient anxiety and performance of unnecessary diagnostic procedures. Disease sites containing teratoma are nearly always 2-deoxy-2-fluoro-D-glucose (FDG)-negative and yet must be regarded as fully malignant metastases equivalent to other histologies (e.g., yolk sac, choriocarcinoma, etc.) and require systemic chemotherapy. The state of the art is to stick with the basics, which, in most cases, consists of a CT scan of the abdomen and pelvis with contrast, either a chest x-ray or CT of the chest, and the tumor markers human chorionic gonadotropin (HCG), alpha-fetoprotein (AFP), and...
TABLE 1. Common Pitfalls in Germ Cell Tumor Management

<table>
<thead>
<tr>
<th>Disease Setting</th>
<th>Pitfall</th>
<th>Danger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic workup</td>
<td>Use of PET scan for staging</td>
<td>Performs no better than CT, yet more expensive and excess radiation exposure; may lead to complacency about FDG-negative masses or overidentification of irrelevant conditions</td>
</tr>
<tr>
<td>Early-stage disease</td>
<td>Management based on pre-orchiectomy tumor markers</td>
<td>Can lead to overtreatment of stage I-A or I-B as I-S</td>
</tr>
<tr>
<td></td>
<td>Lack of recognition of causes of false-positive elevations of AFP or HCG</td>
<td>Can lead to overtreatment of stage I-A or I-B as I-S</td>
</tr>
<tr>
<td></td>
<td>Lack of recognition that borderline lymph nodes in the landing zone may be benign</td>
<td>Can lead to overtreatment of stage I as stage II</td>
</tr>
<tr>
<td>Advanced disease</td>
<td>Management based on pre-orchiectomy tumor marker levels</td>
<td>Can lead to incorrect IGCCCG classification with potential for over- or undertreatment</td>
</tr>
<tr>
<td></td>
<td>Failure to recognize teratoma as the etiology of lack of shrinkage</td>
<td>Can lead to additional chemotherapy beyond three to four cycles and unnecessary toxicity</td>
</tr>
<tr>
<td></td>
<td>Use of PET in postchemotherapy nonseminoma evaluation</td>
<td>Can lead to omission of surgery predisposing to relapse, particularly late relapse with teratoma or secondary somatic malignancy</td>
</tr>
<tr>
<td></td>
<td>Failure to recognize the slow terminal decline rate of HCG in patients with a high starting HCG value</td>
<td>Can lead to unnecessary use of salvage chemotherapy with considerable toxicity</td>
</tr>
<tr>
<td>All phases</td>
<td>Decreasing etoposide or cisplatin doses or substituting carboplatin for cisplatin</td>
<td>Leads to decrease in efficacy (cures and survival)</td>
</tr>
<tr>
<td></td>
<td>Failure to refer patients to expert center (e.g., salvage chemotherapy, need for RPLND, or other complicated situation)</td>
<td>Can lead to a variety of incorrect or insufficient treatments and suboptimal outcome</td>
</tr>
</tbody>
</table>

Abbreviations: GCT, germ cell tumor; FDG, 2-deoxy-2-[18F]fluoro-2-glucose; HCG, human chorionic gonadotropin; AFP, alpha-fetoprotein; IGCCCG, International Germ Cell Cancer Collaborative Group; RPLND, retroperitoneal lymph node dissection.

lactate dehydrogenase. Use of PET scan in GCT management is reserved for evaluation of the large (> 3 cm) residual mass after chemotherapy for seminoma and on an individualized basis in some patients with rising markers without evidence of disease on conventional imaging.

PRACTICAL APPLICATIONS

- Measurement of the tumor markers AFP and HCG is an essential component of GCT management. However, it is critical to use the tumor markers obtained after rather than before orchiectomy for staging, estimation of prognosis, and treatment determination as use of pre-orchiectomy markers can lead to either under- or overtreatment.
- Teratoma, a histologic subtype of nonseminoma that represents terminally differentiated somatic tissue, is chemotherapy-resistant and not associated with tumor marker production or FDG-avidity. PET scan cannot differentiate between teratoma and necrosis and has no routine role in nonseminoma management.
- Nonmalignant causes of (low-level) elevation of HCG (hypogonadism, heterophile antibodies) and AFP (alcohol, heterophile antibodies) should be considered before altering management decisions.
- When HCG starts off in the poor-risk range (> 50,000 mIU/mL), it can exhibit a slow terminal decline rate at the end of chemotherapy. A slowly declining HCG may eventually normalize and does not necessarily represent chemotherapy resistance or the need for salvage chemotherapy.
- Randomized trials demonstrate that lowering the doses of cisplatin or etoposide in first-line chemotherapy leads to inferior outcomes as does substituting carboplatin for cisplatin. These practices should be avoided whenever possible.

EARLY-STAGE DISEASE

Errors in the management of early-stage disease typically stem from a lack of appreciation of the natural history of GCTs nor the potential for mild imaging or serum tumor marker abnormalities to be unrelated to GCTs. An essential principle to remember is that prognosis and management are dictated by the values of postorchiectomy tumor markers (representing the burden of metastatic disease) in patients with testicular GCT. Making decisions based on pre-orchiectomy marker values can lead to both over-and undertreatment. For example, it is not uncommon for marker levels to normalize following orchiectomy, even when the values were quite elevated preoperatively. In the absence of metastatic disease on imaging, such patients have stage I disease and may not require any further treatment. Treatment of such a patient with full-course chemotherapy for advanced disease will result in unnecessary toxicity and long-term risks. It is important to follow declining marker levels to normalization or rise in such situations and knowledge of the half-lives for AFP (5–7 days) and HCG (1–3 days) can be helpful in predicting the likelihood of normalization.

The potential for false-positive low-level elevation of markers is another important consideration in GCT management. For AFP, the upper limit of normal is often between 6 and 8, but a considerable minority of the population will have an AFP in the 10 to 15 range and, more rarely, between 15 to 25. Heterophile antibodies, insults to the liver...
(alcohol, viral hepatitis, or hemochromatosis), and hereditary persistence of AFP are additional non-GCT–related etiologies of mildly elevated AFP.10-12 The marker trend is the key to differentiating such cases from active malignancy. Those that remain stable over several weeks or after cancer-directed intervention such as an orchietomy are typically not of malignant etiology.

False positives for HCG include testosterone deficiency, marijuana usage,13 heterophile antibodies,14,15 and use of some medications. Hypogonadism can cause elevation of HCG via two mechanisms; in less specific assays, increased pituitary secretion of luteinizing hormone secretion in response to low testosterone can cross-react with the assay for HCG due to the substantial homology between luteinizing hormone and HCG.16 Pituitary secretion of HCG, which can also occur in the setting of hypogonadism, is another potential mechanism of nontumor elevation.17 The level rarely exceeds 10 ng/mL, and a testosterone suppression test can quickly establish whether hypogonadism is the cause of HCG elevation in suspected cases.17,18

Another even more common problem surfaces when practitioners are faced with borderline retroperitoneal lymph nodes in a patient who otherwise would be considered to have stage I disease. There is an approximately 30% likelihood that a retroperitoneal lymph node between 1.0 and 1.5 cm in the testicular tumor landing zone (left para-aortic for left testis tumors and interaortocaval for right testis tumors) will be benign. Nodes outside of the landing zone have even a higher chance of being unrelated to GCTs. As such, borderline lymph nodes can often be followed with a repeat CT scan 6 to 8 weeks later.19 If the nodes are continuing to enlarge, then they likely represent metastasis, but if they remain stable or are decreasing in size, then they are probably benign. Repeating imaging can avoid overtreatment and does not compromise cure rates in most patients. One must also appreciate that the natural history of GCTs dictates that 90% to 95% of metastatic testicular GCTs will spread to the retroperitoneum first with only 5% to 10% skipping the retroperitoneum and spreading to other sites such as the lungs, mediastinal or neck lymph nodes, or liver. Thus, when approaching a patient with reported skip metastasis and normal tumor markers, one must consider the possibility of nonmalignant etiologies such as sarcoidosis in the case of mediastinal adenopathy and small lung nodules.20 Biopsy can be helpful in distinguishing these two scenarios.

**ADVANCED DISEASE**

In patients with advanced GCTs, use of pre-orchietomy markers for decision-making again emerges as a common mistake. Similar to staging, the postorchietomy markers must be used to determine International Germ Cell Cancer Collaborative Group prognostic classification that guides chemotherapy selection. It is not uncommon for a patient whose markers are in the intermediate- or poor-risk range pre-orchietomy to decline to the good-risk range following surgery and would be at risk for increased toxicity if treated as having poor-risk disease. In contrast, a patient with pre-orchietomy markers in the good-risk range who has a rapid marker rise postorchietomy to the intermediate- or poor-risk values would be significantly undertreated with a decreased chance of cure if chemotherapy were selected based on the pre-orchietomy values.

A final tumor marker consideration is that at the end of chemotherapy, HCG may exhibit a slow terminal decline rather than following the typical 1- to 3-day half-life we see after surgery and the first two cycles. As shown elegantly by Zon et al,21 patients with prechemotherapy HCG values higher than 50,000 mIU/mL can have a slow decline following completion of their fourth cycle of chemotherapy. More than 50% of men with detectable HCGs that are declining will eventually normalize their HCG values and never require any further chemotherapy.

Another common issue in advanced disease is failure to recognize the importance of teratoma in the postchemotherapy management of nonseminoma. This generally applies to patients who achieve normalization of their markers following chemotherapy but with only a modest decrease in the size of retroperitoneal adenopathy. These patients should not be treated with another two cycles of chemotherapy, given there is no evidence that six cycles is superior to four and that teratoma may explain the lack of radiographic response. Teratoma is not sensitive to chemotherapy such that further chemotherapy is unlikely to garner further reduction in lymphadenopathy and will add toxicity. Instead, surgical resection of the residual nodes should be pursued in this situation. Similarly, PET scan should not be used to evaluate the residual retroperitoneal mass in such cases. Both teratoma and necrosis lack FDG avidity on PET scan, and therefore, a negative PET does not obviate the need for surgical resection.22 Proceed to surgery and “forget the PET.”

A critically important component of advanced GCT management is to ensure proper chemotherapy dosing to maximize patient outcomes. The standard dose for etoposide is 500 mg/m2 per cycle and for cisplatin is 100 mg/m2 per cycle in both the bleomycin, etoposide, and cisplatin and etoposide and carboplatin regimens. Decreasing the doses of either drug has been demonstrated in several studies to lead to inferior outcomes.23,24 Furthermore, substitution of carboplatin for cisplatin also decreases cure rates and survival.25,26 In addition to lower cure rates, salvage chemotherapy adds a substantial burden of therapy and toxicity (neuropathy, tinnitus, hearing loss, infertility, secondary malignancies, and cardiovascular disease) such that deviating from standard dosing that maximizes success should be avoided. Patients should also be treated on time every 21 days whenever possible without unnecessary delays.

A final and perhaps the most important pitfall in managing GCTs is not seeking advice or referring to a high-volume center for complicated or unusual cases or when certain expertise is not available at the local treatment site. This applies to most cases in which retroperitoneal lymph node dissection or salvage chemotherapy is required and particularly for patients in whom high-dose chemotherapy with
autologous stem cell reinfusion is being considered. Referral to a high-volume center will maximize the chance of cure and limit unnecessary complications and toxicity.

CONCLUSION

Although the state-of-the art management of GCTs may not have changed much over the past decade, it is increasingly recognized how deviations from standard care and failure to refer patients to a high-volume center negatively affect outcome. Simply put, state-of-the-art management of GCTs starts by stating that there is an art to managing GCTs, one that is enhanced by experience in every phase of the disease from surgery to chemotherapy to survivorship.

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Management of Refractory Germ Cell Cancer

Anja Lorch, MD

OVERVIEW

Over the past 5 decades, the use of well-validated, guideline-based strategies has resulted in high cure rates in newly diagnosed patients with germ cell cancer (GCC). However, about 30% of those with metastatic disease at initial presentation will experience refractory disease. Salvage treatment is far more complex and less validated than first-line treatment because it is rare, patient cohorts are more heterogeneous, and prognostic factors seem to have greater impact. Prior to the initiation of any salvage treatment, several considerations must be made, including assessment of known prognostic factors and choice of the optimal salvage strategy. Evaluation of patients according to their disease biology, response to prior treatment, and the extent of their tumor burden at the time of salvage treatment is crucial for establishing the optimal salvage strategy. Patients with metastatic germ cell cancer in whom adequate cisplatin-based first-line chemotherapy fails should be included in the ongoing randomized TIGER trial comparing conventional-dose chemotherapy with high-dose chemotherapy as first salvage treatment. Outside this trial, patients may be treated with conventional or high-dose chemotherapy depending on the presence or absence of adverse prognostic factors, availability of resources, and patient and physician preferences.

Special Considerations

Patients who progress or relapse during active surveillance or after adjuvant chemotherapy for stage I disease are no candidates for any salvage treatment. Such patients should be managed according to the algorithms for primary metastatic disease depending on their initial histology and their stage at the time of progression.1

Salvage treatment should also not be given in patients who respond well but remain positive for the serum tumor markers alpha-fetoprotein or human chorionic gonadotrophin after completion of first-line treatment. Although some will eventually progress, others will develop a plateau or even normalize their markers later on and should be scheduled for resection of residual tumors.2 However, if the markers start to increase, salvage chemotherapy is mandatory.3

A dilemma exists for patients with evidence of high percentage of vital tumor after residual tumor resection. On the basis of retrospective analyses and the higher risk for relapse, two additional adjuvant cycles have been recommended by some authors.4 However, the benefit of this approach has never been prospectively validated. Alternatively, close follow-up of such patients can be done, and further treatment can be given only to those patients who progress during follow up.

There are two important subgroups of patients in whom salvage surgery rather than salvage chemotherapy is successful: (1) patients with a “growing teratoma” syndrome during or after first-line chemotherapy who demonstrate radiologic progression but have normalized tumor markers5 and (2) patients with resectable late-relapse GCC that occurs more than 2 years after cisplatin-based first-line chemotherapy.6 They will best benefit from immediate salvage surgery, even despite documented tumor marker increase, usually of alpha-fetoprotein.7 Malignant transformation may be found in such specimens, which remains a challenge with respect to further management.7,8

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Disclosures of potential conflicts of interest provided by the author are available with the online article atasco.org/edbook.

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In the scenario of patients with obvious progression during adequately given cisplatin-based first-line chemotherapy, so-called absolute cisplatin refractory, patients are candidates for salvage chemotherapy instead of “desperation surgery,” as multifocal disease usually is present and long-term remissions using treatment intensification by high-dose chemotherapy (HDCT) followed by salvage surgery can be achieved.9,10

EVALUATION OF PATIENTS PRIOR TO SALVAGE TREATMENT

High accuracy must be given to the definition of refractory, progressive, or relapsed GCC.11 Neither new radiologic lesions alone nor a single elevation of a serum tumor marker should be considered sufficient to initiate salvage chemotherapy. Infrequently, transient elevations of serum tumor markers with spontaneous normalization have been observed, as well as lung changes (e.g., from bleomycin toxicity or manifestations of sarcoidosis) that may likewise be mistaken for progressive disease.

For these reasons, current guidelines require unequivocal demonstration of relapse or progression prior to the initiation of salvage treatment either by serial determination of increasing serum tumor markers or, if absent, by histologic evidence of vital undifferentiated cancer.1,12

PROGNOSTIC FACTORS FOR FIRST SALVAGE CHEMOTHERAPY

Prognostic factors have also been established in patients with refractory or relapsed GCC. These factors usually reflect tumor biology and the extent of disease and can be used to guide treatment decisions.

A recent large collaborative effort of the International Prognostic Factor Study Group that included nearly 1,600 patients in a robust analysis of prognostic factors led to the development of an internationally accepted prognostic score for first salvage chemotherapy.13 This analysis identified seven independent variables with a significant impact on progression-free survival and overall survival. Adverse prognostic factors in this analysis were (1) extragonadal primary tumors, (2) less than complete remission or less than tumor-marker-negative partial remission to first-line treatment, (3) a progression-free interval of 3 months or less, (4) elevation of alpha-fetoprotein at salvage to more than 1,000 ng/mL, (5) elevation of human chorionic gonadotrophin at salvage to more than 1,000 U/L, and (6) the presence of liver, bone, or brain metastases. Patients with pure seminoma represented a separate subgroup (Table 1).

A total of five prognostic categories could be defined.13 Two-year progression-free survival, estimated using the Kaplan-Meier method, was 75% for patients in the very low risk group, 51% in the low-risk group, 40% in the intermediate-risk group, 26% in the high-risk group, and 6% for patients in the very high risk group.13 Despite this improvement in the identification of prognostic factors, future

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**TABLE 1. Prognostic Factors at First Relapse**

<table>
<thead>
<tr>
<th>Histology</th>
<th>Favorable Seminoma</th>
<th>Unfavorable Nonseminoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor location</td>
<td>All, except primary mediastinal nonseminomas</td>
<td>Primary mediastinal nonseminomas</td>
</tr>
<tr>
<td>Response to first-line therapy</td>
<td>CR or PR with negative serum tumor markers</td>
<td>PR with positive serum tumor markers or worse</td>
</tr>
<tr>
<td>Progression-free interval</td>
<td>&gt; 3 months after initiation of the last first-line chemotherapy</td>
<td>&lt; 3 months after initiation of the last first-line chemotherapy</td>
</tr>
<tr>
<td>Metastases at relapse</td>
<td>Lymph node or pulmonary metastases as the only metastatic sites</td>
<td>Extrapulmonary organ metastases (liver, bone, brain)</td>
</tr>
<tr>
<td>Tumor markers at relapse</td>
<td>AFP low (≤ 1,000 ng/mL)</td>
<td>AFP high (&gt; 1,000 ng/mL)</td>
</tr>
<tr>
<td></td>
<td>HCG low (≤ 1,000 U/L)</td>
<td>HCG high (&gt; 1,000 U/L)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission; PR, partial remission; AFP, serum alpha-fetoprotein; HCG, serum human chorionic gonadotropin.

Adapted from Lorch et al.13

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**PRACTICAL APPLICATIONS**

- Approximately 30% of patients with metastatic disease at initial presentation, corresponding to about 5% to 10% of all patients with GCC, will experience refractory disease and need further therapy.
- Several considerations must be made before salvage treatment: verification that first-line treatment has failed, search for metastatic sites and extent of disease, assessment of known prognostic factors, and selections of the optimal salvage strategy.
- Evaluation of patients according to their disease biology, response to prior treatment, and the extent of their tumor burden at the time of salvage treatment is crucial for establishing the optimal salvage strategy.
- Patients with metastatic GCC in whom adequate cisplatin-based first-line chemotherapy has failed should be included in the ongoing randomized TIGER trial comparing CDCT with HDCT as first salvage treatment.
- Outside TIGER, patients may be treated with CDCT or HDCT depending on the presence or absence of adverse prognostic factors, availability of resources, and patient and physician preferences.
challenges will consist of translation into clinical management strategies (Fig. 1).

CONVENTIONAL-DOSE CHEMOTHERAPY
Depending on prognostic factors and careful patient selection, conventional-dose chemotherapy (CDCT) will successfully salvage about 15% to 70% of patients at the time of their first salvage attempt. The regimens combine cisplatin and ifosfamide with either etoposide (VIP), vinblastine, or paclitaxel, with none of these regimens being clearly superior to the others.14-16 To date, four cycles of cisplatin/ifosfamide/paclitaxel, VIP, or cisplatin/ifosfamide/vinblastine should be considered standard as a first salvage CDCT regimen (Table 2).

HDCT AND THE SEARCH FOR AN OPTIMAL HDCT COMBINATION
Unsatisfactory results with CDCT, particularly in patients presenting with adverse prognostic factors, led to the use of HDCT followed by the reinfusion of autologous hematopoietic stem cells, a technique that was pioneered in the early 1990s.20 Nichols et al17 in 1989 first reported on a combination of high-dose carboplatin and etoposide that achieved a high response rate and long-term remission in patients with refractory GCCs that had not responded to prior CDCT. This initial report triggered a large number of subsequent trials in the United States and Europe that were able to reproduce these results in independent patient cohorts.18,19,21

Despite all subsequent efforts, the initial combination of carboplatin and etoposide is still the mainstay of all HDCT regimens. Several studies investigated modifications either by using higher doses or by incorporating additional drugs, such as cyclophosphamide, ifosfamide, and thiotepa. Although none of these trials delivered unequivocal clinical evidence of improved efficacy, many of these attempts resulted in considerable increases in adverse effects.21 Recent phase II trials reporting impressive results from new combinations and/or the addition of the antiangiogenic drug bevacizumab are limited by small sample sizes and heterogeneous patient populations.22,23 In contrast to these attempts, improvements in supportive care and the use of peripheral blood progenitor cells led to a substantial reduction in the time to hematopoietic recovery and thus to a reduction in the treatment-related mortality rate from more than 10% to 3% or less in the most recent series.20

### TABLE 2. Standard First Salvage Chemotherapy Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose</th>
<th>Application</th>
<th>No. of Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDCT14,15</td>
<td>VIP</td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>75 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td>TIP</td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175–250 mg</td>
<td>Day 1</td>
</tr>
<tr>
<td>VeIP</td>
<td>Cisplatin</td>
<td>20 mg/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td></td>
<td>Ifosfamide</td>
<td>1.2 g/m²</td>
<td>Days 1–5</td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>0.11 mg/kg</td>
<td>Days 1 and 2</td>
</tr>
<tr>
<td>HDCT17-19</td>
<td>Carboplatin</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>500 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>AUC 8</td>
<td>Days 1–3</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>400 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>700 mg/m²</td>
<td>Days 1–3</td>
</tr>
<tr>
<td></td>
<td>Etoposide</td>
<td>750 mg/m²</td>
<td>Days 1–3</td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the plasma drug concentration-time curve; CDCT, conventional-dose chemotherapy; HDCT, high-dose chemotherapy; TIP, cisplatin, ifosfamide, and paclitaxel; VeIP, cisplatin, ifosfamide, and vinblastine; VIP, cisplatin, ifosfamide, and etoposide.

![FIGURE 1. Overall Survival Probability After First Salvage Treatment According to Prognostic Factors](image-url)
SEQUENTIAL HDCT VERSUS SINGLE HDCT

The comparison of single HDCT using three drugs and sequential HDCT using the standard backbone carboplatin and etoposide has been carried out in a large prospective, randomized, multicenter phase III trial by the German Testicular Cancer Study Group.21,24 A total of 216 patients with relapsed and/or refractory GCC were randomized to either one cycle of conventional-dose VIP followed by three cycles of high-dose carboplatin and etoposide or to three cycles of conventional-dose VIP followed by one cycle of high-dose carboplatin, etoposide, and cyclophosphamide.21 Both treatment regimens showed similar results with respect to efficacy. Progression-free survival after 2 years was reported as 52% and 47% for the two treatment arms, and overall survival after 2 years was 58% and 50%, respectively. However, the trial had to be terminated early because of treatment-related excess mortality of 16% in the single HDCT arm versus 4% in the sequential HDCT arm. Long-term follow-up of patients from this trial confirmed these results.24 As a consequence, most centers worldwide use sequential rather than single HDCT, with two or three HDCT cycles combining carboplatin and etoposide (Table 2).18,19,21

Both strategies of two cycles of HDCT as published by investigators from Indiana University and three cycles of HDCT as published by investigators from the Memorial Sloan Kettering Cancer Center and the German Testicular Cancer Study Group are well founded and equivalent according to current knowledge.

CDCT OR HDCT AS FIRST SALVAGE TREATMENT

The routine use of HDCT as first-line salvage chemotherapy in patients with GCC remains controversial and is the subject of ongoing research.

In a thoroughly conducted matched-pair analysis taking into account all prognostic factors known at that time, it was demonstrated that the use of HDCT as part of first salvage therapy led to an improvement of approximately 10% in terms of both event-free survival and overall survival.25 Other groups have also suggested that HDCT may be superior to CDCT as first salvage treatment. In a retrospective analysis of 135 patients from Indiana University, Einhorn et al18 reported long-term survival probabilities following sequential HDCT of about 70% across all risk categories. A prospective study of 81 patients from the Memorial Sloan Kettering Cancer Center with adverse prognostic features prior to first salvage treatment demonstrated that two cycles of CDCT with paclitaxel and ifosfamide followed by three cycles of HDCT with carboplatin and etoposide resulted in an overall survival probability of about 50% at 5 years.19 More recently, an international group of investigators retrospectively compared CDCT with HDCT in the largest cohort of first salvage patients with GCC reported to date. HDCT outperformed CDCT in almost all of the prognostic subgroups with respect to progression-free and overall survival.26

A rare clinical scenario occurs in patients with unresectable widespread metastatic late relapses. In such patients CDCT with cisplatin/ifosfamide/paclitaxel as well as sequential HDCT with carboplatin and etoposide have both been successfully used.27-29

In contrast, the only phase III trial (IT94) that prospectively compared CDCT with HDCT failed to demonstrate a statistically significant difference between the two strategies.30 In this multicenter trial across several European countries, 263 patients were randomly assigned to receive either a single cycle of HDCT after three cycles of conventional-dose VIP or four cycles of conventional-dose VIP alone. The IT94 trial has been criticized for methodological reasons and is not conclusive to stop the debate over optimal first salvage strategy.

Therefore, in a transatlantic multicenter collaborative effort between the Alliance for Clinical Trials in Oncology in the United States and the European Organisation for Research and Treatment of Cancer in Europe, the question of CDCT versus HDCT is currently being addressed in a prospective randomized trial comparing four cycles of cisplatin/ifosfamide/paclitaxel versus sequential HDCT (TIGER trial; NCT02375204).31

SECOND OR SUBSEQUENT SALVAGE TREATMENT

Although long-term remissions and cure can still be achieved in individual patients, long-term survival probabilities are poor in patients who experience multiple relapses or who progress despite adequate first salvage chemotherapy. One retrospective analysis in 49 patients who received HDCT as second or subsequent relapse therapy demonstrated that the long-term survival probability was reduced to less than 20%, but long-term remissions could be achieved.32 Therefore, unless contraindicated, HDCT is recommended even in patients who have failed to respond to multiple previous conventional treatments.

Conventional-dose treatment with newer agents such as oxaliplatin and gemcitabine alone or in combination with paclitaxel as well as others has also been studied in patients with multiple relapses and reported to occasionally induce long-term remissions, but these approaches have not been formally compared with a strategy of HDCT as a second or subsequent salvage attempt.33-36

FUTURE DIRECTIONS

Recently, the role of targeted therapies has been evaluated in several phase II trials in patients not responding to CDCT and/or HDCT. Sunitinib, everolimus, or bevacizumab reached objective responses or met their primary endpoints.

Currently the role of immunotherapy is explored in patients with refractory GCC.37-40 First results of a phase II trial with pembrolizumab, an anti–PD-1 antibody, did not show clinically meaningful single-agent activity.41

To date, additional studies are evaluating the role of other targeted agents, for example the cyclin-dependent kinase inhibitor palbociclib (NCT01037790), the PARP-1 inhibitor olaparib (NCT02537651), and the anti-CD30 monoclonal antibody brentuximab (NCT02689219).
CONCLUSIONS
Evaluation of patients according to their disease biology, response to prior treatment, and the extent of their tumor burden at the time of salvage treatment is crucial for establishing the optimal salvage strategy. First, refractory response to prior treatment, and the extent of their tumor burden. Second, patients with growing teratoma or with resectable late relapses must be scheduled for upfront salvage surgery rather than salvage chemotherapy. Third, all other patients with metastatic GCC in whom adequate cisplatin-based first-line chemotherapy fails should be included in the ongoing randomized TIGER trial comparing CDCT with HDCT as first salvage treatment. Outside this trial, patients may be treated with CDCT or HDCT depending on the presence or absence of adverse prognostic factors, availability of resources, and patient and physician preferences. It is of importance that all those patients be referred and treated at or in close cooperation with centers that have special expertise in this rare group of patients.

References


Personalized Management of Advanced Kidney Cancer

Jeffrey Graham, MD, Daniel Y. C. Heng, MD, James Brugarolas, MD, PhD, and Ulka Vaishampayan, MD

OVERVIEW

The treatment of renal cell carcinoma represents one of the great success stories in translational cancer research, with the development of novel therapies targeting key oncogenic pathways. These include drugs that target the VEGF and mTOR pathways, as well as novel immuno-oncology agents. Despite the therapeutic advancements, there is a paucity of well-validated prognostic and predictive biomarkers in advanced kidney cancer. With a number of highly effective therapies available across multiple lines, it will become increasingly important to develop a more tailored approach to treatment selection. Prognostic clinical models, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, are routinely used for prognostication in clinical practice. The IMDC model has demonstrated a predictive capability in the context of these treatments including immune checkpoint inhibition. A number of promising molecular markers and gene expression signatures are being explored as prognostic and predictive biomarkers, but none are ready to be widely used for treatment selection. In this review, we will explore the current landscape of personalized care in metastatic renal cell carcinoma. This will include a focus on both prognostic and predictive factors as well as clinical applications of biology in kidney cancer.

The treatment of renal cell carcinoma (RCC) has undergone a dramatic evolution over the last decade. The improvements in treatment are secondary to a better understanding of the biologic factors driving cancer growth. The elucidation of the importance of the VEGF and mTOR pathways led to the introduction of several novel agents in the treatment of metastatic renal cell carcinoma (mRCC). More recently, several new immuno-oncology agents have shown impressive activity in advanced kidney cancer and are currently being explored in combination with targeted therapy. The evolution of targeted therapy as the mainstay of management in RCC has been a dominant part of the advances.

Despite these impressive successes in exploiting molecular targets, there has been a paucity of biomarkers in RCC that can predict response or clinical outcomes with the novel agents. As the number of therapeutic options increases, it is critical to develop a personalized strategy to treatment, taking into consideration both tumor and patient characteristics to develop a tailored treatment plan. In a disease such as RCC where the spectrum of overall survival (OS) ranges from a few months to many years even without administration of any systemic therapy, the risk prognostication of the patients is of paramount importance in therapeutic decision making. Individualized care using predictive biomarkers is central to the treatment of other advanced malignancies. This includes the anti-HER2 antibody in HER2-amplified breast cancer, anti-EGFR therapies in KRAS wild-type colorectal cancer, and BRAF inhibitors in BRAF mutant melanomas. Thus, the elucidation of predictive factors is an unmet need in mRCC and an area of active research.

In this review, we will explore the current landscape of personalized care in mRCC. This will include a focus on both prognostic and predictive factors as well as clinical applications of biology in kidney cancer. We will provide examples of a personalized approach to systemic therapy and explore future directions in the individualized treatment of advanced kidney cancer.

OVERVIEW OF PROGNOSTIC CLINICAL FACTORS

A personalized approach to the treatment of cancer necessitates an understanding of the variables influencing prognosis. Prior to the advent of targeted agents, a commonly used prognostic risk index was the Memorial Sloan Kettering Cancer Center model. This model was developed and validated in the era of interferon therapy, and it incorporated a number of clinical and biochemical variables. The Memorial Sloan Kettering Cancer Center model integrated five adverse factors: Karnofsky performance status of less than 80%, elevated lactate dehydrogenase, high corrected serum calcium, low hemoglobin, and interval from diagnosis to treatment of less than 1 year. Based on the number of pretreatment factors, three prognostic groups were identified:
were identified as having prognostic significance in this population. These included two clinical factors (a Karnofsky performance status of less than 80% and time from diagnosis to initiation of therapy of less than 1 year) as well as four laboratory factors (hemoglobin below the lower limit of normal and elevated corrected calcium, neutrophil count, and platelet counts greater than the upper limit of normal). The final IMDC model was able to successfully stratify real-world patients into three distinct prognostic groups: favorable (zero risk factors), intermediate (one to two risk factors), and poor risk (more than two risk factors). Table 1 summarizes the Memorial Sloan Kettering Cancer Center and IMDC prognostic models.

The IMDC model was externally validated using a cohort of 1,028 real-world patients from 13 international cancer centers. In this analysis, the median OS associated with each prognostic group was 43 months, 23 months, and 8 months in the favorable, intermediate, and poor risk groups, respectively. The IMDC model continues to be widely used to stratify patients in contemporary clinical trials and to provide personalized, risk-directed treatment selection in everyday clinical practice. The recent trials of nivolumab, cabozantinib, and ipilimumab and nivolumab as well as lenvatinib and everolimus have used the IMDC criteria, as they were specifically applicable to anti-VEGF therapy with suntinib.

Since the initial validation of the IMDC model, it has been studied in a number of other populations of patients with RCC. Similar to the first-line setting, the IMDC model has been demonstrated to provide prognostic stratification in both the second and third-line settings. Because the original IMDC model included predominately clear cell renal cell carcinoma (ccRCC), Kroeger et al examined the applicability of the IMDC prognostic model in advanced non–clear cell renal cell carcinoma (nccRCC). In this population, patients with nccRCC had inferior OS (12.8 vs. 22.3 months) compared with patients with ccRCC. Similar to the clear cell population, the IMDC model was able to reliably stratify the nccRCC cohort into three distinct prognostic groups. More recently, the IMDC was shown to provide prognostic stratification among patients receiving second-line immunotherapy agents, including the immune checkpoint inhibitor nivolumab.

Given that the IMDC prognostic model did not include patients receiving pazopanib, Perez-Valderrama et al conducted a retrospective observational study to validate the model in this population. The study included 278 patients treated with first-line pazopanib for mRCC in 34 centers in Europe. Within this cohort, 19.4% had favorable risk, 57.2% had intermediate risk, and 23.4% had poor risk. As with first-line suntinib, the IMDC model was able to estimate the prognosis of patients treated with first-line pazopanib. The median OS was not reached in the favorable risk group and was 21.6 months and 7.1 months in the intermediate and poor risk groups, respectively.

Beyond the aforementioned variables included in the IMDC model, there have been a number of other clinical factors demonstrated to have prognostic significance in advanced kidney cancer. These include the baseline neutrophil-to-lymphocyte ratio (NLR) and the presence of bone and liver metastases. McKay et al examined the
prognostic impact of bone and liver metastases in a retrospective analysis of 2,027 patients with mRCC treated with first-line targeted therapy. Both of these factors were associated with inferior outcomes, with hazard ratios (HR) of 1.38 and 1.37 (p < .0001) for the presence of bone and liver metastases, respectively. Elevated markers of systemic host inflammation, such as NLR, have been shown to be associated with a poor prognosis in several solid tumors. Templeton et al13 explored the impact of baseline NLR on survival in advanced RCC. In this analysis, higher NLR at baseline was associated with shorter OS (adjusted HR per 1-unit increase in lnNLR, 1.69; 95% CI, 1.46–1.95; p < .001).13

Although uncovering variables associated with poor prognosis is important in developing personalized treatment strategies, identifying factors that do not influence clinical outcomes is also helpful. As the overall life expectancy of our population increases, understanding the impact of age on cancer outcomes will become increasingly important. Khambati et al14 explored the use of first-line targeted therapy in elderly patients (older than age 75) with mRCC. In this analysis, outcomes were found to be similar between the older and younger subgroups, even when adjusted for known poor prognostic factors. These findings suggest that age alone should not be used as an absolute contraindication to targeted therapy.

TABLE 2. Results of the CABOSUN Trial: Cabozantinib Versus Sunitinib in First-Line mRCC, With Outcomes by Subgroup Analysis Including IMDC Risk Group and Presence of Bone Metastases

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CABO (79 Patients)</th>
<th>SUN (78 Patients)</th>
<th>HR (95% CI) p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>46 (34–57)</td>
<td>18 (10–28)</td>
<td>0.66 (0.46–0.95) .012</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>8.2 (6.2–8.8)</td>
<td>5.6 (3.4–8.1)</td>
<td>0.54 (0.31–0.95) .012</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>6.14</td>
<td>3.38</td>
<td>0.54 (0.31–0.95) .012</td>
</tr>
<tr>
<td>Poor IMDC risk</td>
<td>6.14</td>
<td>2.77</td>
<td>0.75 (0.35–1.65) .012</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>8.31</td>
<td>6.24</td>
<td>0.64 (0.43–0.96) .012</td>
</tr>
<tr>
<td>Median OS, months (95% CI)</td>
<td>30.3 (14.6–35)</td>
<td>21.8 (16.3–27)</td>
<td>0.8 (0.50–1.26) .012</td>
</tr>
</tbody>
</table>

Abbreviations: mRCC, metastatic renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; HR, hazard ratio; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.

OBSERVATION/SURVEILLANCE OF THE PATIENT WITH METASTATIC RENAL CELL CARCINOMA

mRCC is a heterogeneous disease and one that is characterized by a variable natural history. There appears to be a certain subset of patients with mRCC who may display a less aggressive and more indolent pattern of progression. Given these observations, there has been ongoing interest in the idea of deferred systemic therapy with active surveillance, in contrast to the more standard approach of starting therapy immediately at the onset of metastatic disease. This deferred approach has been examined in a number of retrospective analyses as well as prospectively in a large observational registry, the Metastatic Renal Cell Cancer Registry.15,16 Park et al17 performed a retrospective analysis of 58 patients undergoing active surveillance for mRCC. In this series, the median time to disease progression was 12.4 months. Multivariable analysis revealed that Karnofsky performance status of less than 100%, liver metastases, and time from diagnosis to the start of surveillance of less than 1 year were associated with a shorter time to progression. Importantly, the response rate and OS for the subsequent systemic treatment after surveillance were comparable with those of previous reports.

Rini et al18 conducted a prospective phase II trial designed to examine the feasibility and safety of an initial active

TABLE 3. CheckMate 214: Outcomes in the IMDC Intermediate/Poor Risk Groups and by PD-L1 Expression

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Nivo/Ipi (425 Patients)</th>
<th>SUN (422 Patients)</th>
<th>HR   p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, months (95% CI)</td>
<td>NR (28.2–NE)</td>
<td>26.0 (22.1–NE)</td>
<td>0.63 &lt; .0001</td>
</tr>
<tr>
<td>PD-L1 &lt; 1% (562 patients)</td>
<td>NR (28.2-NE)</td>
<td>NR (24-NE)</td>
<td>0.73 .0249</td>
</tr>
<tr>
<td>PD-L1 &gt; 1%</td>
<td>NR (NE-NE)</td>
<td>19.6</td>
<td>0.49 .0003</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>11.6 (8.7–15.5)</td>
<td>8.4 (7.0–10.8)</td>
<td>0.82 .0331</td>
</tr>
<tr>
<td>PD-L1 ≥ 1%</td>
<td>22.8 (9.4–NE)</td>
<td>5.9 (4.4–7.1)</td>
<td>0.48 .0003</td>
</tr>
<tr>
<td>PD-L1 &lt; 1%</td>
<td>11.0 (8.1–14.9)</td>
<td>10.4 (7.5–13.8)</td>
<td>1.0 .9670</td>
</tr>
<tr>
<td>Confirmed ORR, % (95% CI)</td>
<td>42 (37–47)</td>
<td>27 (22–31)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PD-L1 ≥ 1%</td>
<td>58 (48–68)</td>
<td>22 (15–31)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PD-L1 &lt; 1%</td>
<td>37 (32-43)</td>
<td>28 (23-34)</td>
<td>.0252</td>
</tr>
</tbody>
</table>

Abbreviations: IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; Nivo/Ipi, nivolumab/ipilimumab; HR, hazard ratio; OS, overall survival; NR, not reported; NE, not estimable; PFS, progression-free survival; ORR, objective response rate.
surveillance approach in the era of modern targeted therapy. They included patients with asymptomatic mRCC, measurable disease, and no prior systemic therapy. In total, 52 patients were enrolled into the study. Patients were radiographically assessed at baseline and then every 3 months for year 1, every 4 months for year 2, then every 6 months thereafter. The decision to initiate systemic therapy was at the discretion of the treating physician and patient. The median surveillance time until initiation of systemic therapy was 14.9 months. Multivariate analysis showed that a higher number of IMDC risk factors (p = 0.0403) and a greater number of metastatic sites (p = 0.0414) were associated with a shorter surveillance period. Based on this, the authors identified a favorable subgroup, defined as patients with zero to one IMDC risk factor and fewer than two organs with metastatic disease, who had an estimated median surveillance time of 22.2 months. These findings suggest that deferred initiation of systemic therapy using an active surveillance protocol may be appropriate for carefully selected patients with low-risk disease.

**MANAGEMENT OF OLIGOMETASTATIC RENAL CELL CARCINOMA**

Despite improvements in systemic therapy options, local therapy to sites of metastatic disease remains an important component in the personalized management of mRCC. These therapies can include surgical resection (metastasectomy), definitive radiotherapy, and other ablative procedures. The most common sites of metastatic disease in RCC are the lung (45%), bone (30%), lymph nodes (20%), liver (20%), adrenal gland (9%), and brain (8%). For each of these sites, there is evidence that local therapies may be effective, particularly in the setting of a limited number of metastases. In a series of 141 patients treated with metastasectomy in the pretargeted therapy era, curative intent resection was associated with a 44% 5-year OS rate. A disease-free interval greater than 12 months from the time of nephrectomy, solitary site (vs. multiple sites) of metastasis, and age younger than 60 were associated with improved survival.

With regard to resection of pulmonary metastases, Pfannschmidt et al. retrospectively analyzed 191 patients with pulmonary metastases from RCC who underwent surgical resection. The 5-year survival rate after complete metastasectomy was 41.5%. Favorable prognostic factors included having fewer than seven metastatic lesions and a disease-free interval of greater than 23 months. Pancreatic metastases also tend to have a favorable outcome after resection. Solitary bone and soft tissue metastases should also be considered for local therapy. Embolization of metastases, especially bone metastasis, prior to resection is strongly advised to reduce the risk of hemorrhage and complications.

The role of local therapy in the management of RCC is rapidly increasing. Noninvasive techniques such as stereotactic radiation therapy or cryotherapy are increasingly being applied for oligometastatic disease and for consolidative control of residual masses after systemic therapy. Aoun et al. reported on cryoablation of more than 2,000 tumor masses including metastatic sites and renal masses and established efficacy of the procedure. The successful experience with a series of patients specifically with advanced kidney cancer treated with cryotherapy has helped establish the safety, feasibility, and efficacy of this procedure. Wang et al. evaluated stereotactic ablative radiation therapy for extracranial RCC metastases and reported results on 175 metastatic foci, where they observed 1-year local control rates in excess of 90%. There are also emerging data on abscopal effects and of synergy between immunotherapy and ablative techniques as a result of the release of neoantigens. Currently, clinical trials evaluating the direct and abscopal clinical effects and immune changes with a combination of radiation or cryotherapy and immune checkpoint inhibition are in development.

The role of systemic therapy following complete resection of metastatic disease is unclear. The ECOG 2810 phase III trial is comparing adjuvant pazopanib with placebo after metastasectomy and may help clarify the use of targeted agents in resected mRCC. Other trials exploring immune checkpoint inhibitors also allow the inclusion of patients with completely resected metastatic disease, such as KEYNOTE-564, which compares pembrolizumab with placebo in the adjuvant setting, or IMmotion010, which evaluates atezolizumab.

**CLINICAL APPLICATION OF PROGNOSTIC AND PREDICTIVE FACTORS IN FRONTLINE THERAPY OF METASTATIC RENAL CELL CARCINOMA**

In the first-line setting, there are a number of established therapeutic options in mRCC. These include VEGF-targeted drugs (e.g., sunitinib, pazopanib, and cabozantinib), mTOR inhibitors, high-dose interleukin (IL)-2, and more recently, immuno-oncology agents. One of the cornerstones of personalized care in oncology is the discovery and validation of factors that can predict response to various therapeutic agents. These can include clinical or patient-specific factors as well as tumor-specific biomarkers. In this section, we will review clinical factors that may be used to help establish a more personalized approach to the treatment of advanced RCC.

Prognostic clinical factors are important in guiding treatment decisions in mRCC. In 2007, Hudes et al. conducted a phase III randomized trial exploring the role of the mTOR inhibitor temsirolimus in previously untreated, poor-risk, advanced RCC. In this trial, 626 patients were randomly assigned to temsirolimus, temsirolimus plus interferon-alfa, or interferon-alfa monotherapy. Inclusion criteria necessitated that patients have at least three of the following six predictors of poor prognosis: elevated lactate dehydrogenase, elevated serum calcium, low hemoglobin, time from diagnosis to randomization of less than 1 year, Karnofsky performance status of 60 or 70, and metastases in multiple organs. In this poor-risk population, temsirolimus significantly prolonged the median OS compared with interferon-alfa as a single
agent (10.9 vs. 7.3 months; HR for mortality, 0.73; 95% CI, 0.58–0.92). These results led the U.S. Food and Drug Administration to approve temsirolimus in the first-line setting for patients with a poor prognosis. Although this trial did not directly compare the use of an mTOR inhibitor among patients with good-intermediate versus poor risk, it did provide a risk-directed approach to treatment selection. It is important to note that the prognostic index used in this trial is different from the IMDC model. In real-world practice, the use of temsirolimus in this setting is limited as a result of intravenous administration.

Role of Cytoreductive Nephrectomy in Metastatic Renal Cell Carcinoma

Selecting patients with advanced kidney cancer that may benefit from a cytoreductive nephrectomy (CN) is another important decision in the personalized treatment of this population. In the pretargeted therapy era, a combined analysis of two prospective randomized clinical trials revealed that CN followed by interferon treatment was associated with a 5.8-month increase in OS versus interferon alone (13.6 vs. 7.8 months). Unfortunately, there has been a lack of randomized trials exploring the role of CN for patients with mRCC being treated with molecularly targeted therapy. To investigate this further, a retrospective analysis was performed to address the survival benefit of CN for patients with mRCC treated with targeted therapy. The median OS for patients with CN versus without CN was 20.6 versus 9.5 months (p < .0001). When adjusted for IMDC risk criteria to correct for imbalances, the HR of death was 0.60 (95% CI, 0.52–0.69; p < .0001). Importantly, patients who possessed four or more of the IMDC prognostic factors did not appear to benefit from CN. Thus, not all patients should be offered this procedure and the decision should be individualized based on prognosis. In the real world, other considerations include bulk of tumor burden outside of the kidney, brain/liver metastases, symptoms from the primary tumor, and surgical feasibility.

In the recently reported SURTIME trial, investigators attempted to determine whether the sequence of CN among
patients who receive sunitinib has an effect on patient outcomes.\textsuperscript{31} In this trial, patients with metastatic ccRCC were randomly assigned to immediate CN followed by sunitinib versus three cycles of sunitinib followed by CN plus sunitinib (deferred CN). As a result of poor accrual, the investigators decided to report the progression-free rate at week 28 as the primary endpoint. No significant difference between the two groups was observed; the progression-free rate was 42.0\% (95\% CI, 28.2–56.8) versus 42.9\% (95\% CI, 28.8–57.8) in the immediate and deferred arms, respectively (p > .99). Although the study was not adequately powered, an OS improvement was seen for deferred CN. The authors concluded that the deferred approach initiates therapy quickly, does not lead to the inability to perform CN, and CN after sunitinib appears to be safe.

**On-Treatment Predictors of Response**

Given the relative lack of well-validated predictive biomarkers, there has been interest in examining the use of on-treatment predictors of response. Most of these rely on mechanism-based adverse events that may act as a surrogate for clinical efficacy, focusing mainly on VEGF-targeted therapies. This class of drugs has specific toxicities, many of which have been analyzed as potential surrogate biomarkers. These include hypertension, hypothyroidism, neutropenia, thrombocytopenia, and hand-foot syndrome.\textsuperscript{32} The most well established of these adverse events is treatment-related hypertension.\textsuperscript{33} This side effect is common with sunitinib, occurring in approximately one-third of patients.\textsuperscript{34} Rini et al\textsuperscript{35} examined the association between sunitinib-induced hypertension and antitumor efficacy in a large retrospective, pooled analysis of four studies that included 544 patients with mRCC. In this study, hypertension was defined as a systolic blood pressure of at least 140 mmHg or a diastolic blood pressure of at least 90 mmHg. Systolic hypertension was associated with an ORR of 54.8\% compared with an ORR of 8.7\% for patients without systolic hypertension (p < .001). PFS (12.5 vs. 2.5 months; p < .001) and OS (30.9 vs. 7.2 months; p < .001) were also significantly longer for patients with systolic hypertension than for those without. Importantly, the incidence of hypertension-associated end organ dysfunction, such as cardiovascular events, was low. Although retrospective in nature, these findings suggest that treatment-induced hypertension may be a viable predictive biomarker of efficacy in mRCC. Other studies suggest that the phenomenon is generalizable to other anti-VEGF receptor therapies. Inasmuch as the hypertension is likely related to the magnitude of systemic VEGF receptor blockade, higher rates of hypertension may reflect higher effective drug levels.

**CLINICAL APPLICATION OF PROGNOSTIC AND PREDICTIVE FACTORS IN SECOND-LINE THERAPY AND BEYOND OF RENAL CELL CARCINOMA**

In the second-line setting, there are again a number of potential treatment options. These include targeted drugs such as axitinib, cabozantinib, lenvatinib plus everolimus, and the checkpoint inhibitor nivolumab. The optimal sequence of therapy is still an area of active research. Al-Marrawi et al\textsuperscript{36} used the IMDC data set to retrospectively investigate the association of clinical outcome between two lines of targeted therapy. In this study, 464 patients who received both a first- and second-line VEGF inhibitor were included. In this analysis, there was no correlation between first- and second-line responses, in terms of both ORR and PFS. For the entire group, the ORR for first-line therapy was 22\% compared with 11\% for the second-line therapy. These results suggest that in clinical practice, a patient’s response, or lack thereof, should not necessarily influence the choice of second-line targeted therapy.

The phase III METEOR trial helped establish cabozantinib as an effective second-line option in mRCC.\textsuperscript{37} In this trial, 658 previously treated patients were randomly assigned to receive cabozantinib (60 mg/day) or everolimus (10 mg/day). All patients had progressed after receiving prior VEGF tyrosine kinase inhibitor therapy; 69\% of patients had received only one prior course of systemic therapy, whereas 31\% had been treated with two or more prior regimens. Patients progressing while treated with immune checkpoint inhibitors were also included. Randomization was stratified according to the number of previous VEGF tyrosine kinase inhibitors and prognostic risk category. Cabozantinib was associated with an improved PFS compared with everolimus (7.4 vs. 3.8 months), with a corresponding HR of 0.58 (95\% CI, 0.45–0.75; p < .001). This PFS benefit was consistently observed in prespecified subgroups defined according to the number of prior VEGF tyrosine kinase inhibitors and prognostic risk category. A dedicated subset analysis of patients with bone metastases also revealed improved outcomes with cabozantinib.\textsuperscript{38} In this subgroup, the PFS was 7.4 months for cabozantinib versus 2.7 months for everolimus (HR 0.33; 95\% CI, 0.21–0.51). Median OS was also longer with cabozantinib (20.1 vs. 12.1 months; HR 0.54; 95\% CI, 0.34–0.84). These results are consistent with those from the previously discussed CABOSUN trial and suggest that cabozantinib is an effective treatment option for this specific patient population.

Another recently approved second-line option in mRCC is the immune checkpoint inhibitor nivolumab. In the CheckMate 025 trial, 821 patients were randomly assigned to nivolumab (3 mg/kg every 2 weeks) or everolimus (10 mg/day), with all patients having received one or two prior antiangiogenic therapies.\textsuperscript{39} Randomization was stratified by the prognostic risk group and the number of previous antiangiogenic therapy regimens. Nivolumab was associated with a significant improvement in OS (25.0 vs. 19.6 months; HR 0.73). The ORR was also greater with nivolumab compared with everolimus (25\% vs. 5\%). Expression of PD-L1 on tumor cells was not associated with a survival benefit to nivolumab, because those with 1\% or greater expression and those with less than 1\% expression had a similar survival benefit compared with everolimus. Among patients with 1\% or greater PD-L1 expression, the median OS was 21.8
months (95% CI, 16.5–28.1) in the nivolumab group and 18.8 months (95% CI, 11.9–19.9) in the everolimus group (HR 0.79; 95% CI, 0.53–1.17). Higher levels of PD-L1 expression appeared to be associated with shorter OS irrespective of treatment arm. A substantial improvement in quality of life was also observed over the 2-year study period during nivolumab treatment. A dedicated subgroup analysis of this trial has also been reported. This has confirmed a benefit to nivolumab across a number of key baseline factors, including risk groups, age, number and sites of metastases, and type and duration of prior therapy. Duration of response to prior anti-VEGF therapy and NLR (cutoff greater than or less than three) were noted to be independent predictors of benefit from nivolumab therapy in pretreated RCC. In the context of immune therapy, no clear predictive or prognostic factors have emerged that have been correlated in large populations. Exploration of the IMDC database to evaluate prognostic criteria with immunotherapy treatment is ongoing.

**CLINICAL APPLICATIONS OF BIOLOGY IN RENAL CELL CARCINOMA**

The treatment of RCC represents one of the great success stories in translational cancer research, with the development of novel therapies targeting key oncogenic pathways. Despite these advancements, there is a relative lack of well-validated prognostic and predictive molecular biomarkers in advanced kidney cancer.

Broadly speaking, RCC represents a diverse collection of distinct histologic subtypes, with ccRCC comprising more than 75% of cases. Molecular heterogeneity within these subtypes is likely playing an important role in the diversity of responses and resistance to targeted therapies and has complicated biomarker discovery. The elucidation and subsequent clinical validation of these molecular markers will be critical in the development of a more personalized approach to treatment. In this section, we will highlight the contemporary clinical applications of biology in RCC. We will focus on potential molecular prognostic biomarkers as well as predictive factors related to VEGF-targeted therapy and immune checkpoint inhibitors.

**Prognostic Biomarkers**

Advancements in modern genomic techniques, including next-generation sequencing, have revealed the diverse spectrum of both genetic and epigenetic changes in kidney cancer. The most commonly mutated gene in ccRCC is von Hippel Lindau (VHL), which in inactivated in more than 50% of patients with ccRCC. This gene resides on chromosome 3p25 and is essential to the regulation of hypoxia-inducible factor α and angiogenesis. Three other tumor suppressor genes (PBRM1, SETD2, and BAP1) are also located on chromosome 3p and together constitute the most frequently mutated genes after VHL. All three of these genes appear to be involved in regulating epigenetic processes such as chromatin and histone modification. Interestingly, whereas mutations in PBRM1 and BAP1 tend to be mutually exclusive, mutations in PBRM1 and SETD2 appear to synergize.

The prognostic significance of many of these genes has been an area of active research. Kapur et al performed a retrospective analysis of 145 patients with ccRCC at The University of Texas Southwestern Medical Center, the majority of whom had localized or locoregional disease. Their results demonstrated that patients with tumors harboring BAP1 mutations had significantly reduced median OS compared with those who had tumors containing PBRM1 mutations (4.6 vs. 10.6 years, respectively; HR 2.7; p = .04). They observed similar results in analysis of a second cohort (with 327 patients) from The Cancer Genome Atlas (TCGA). Hakimi et al performed a similar study looking at 188 patients who underwent resection of primary ccRCC at the Memorial Sloan Kettering Cancer Center, as well as an independent cohort of 421 patients from the TCGA. BAP1 mutations were associated with worse cancer-specific survival, with an HR of 7.71 (p = .002). PBRM1 mutations appeared to have no impact on cancer-specific survival, whereas SETD2 mutations were associated with worse cancer-specific survival only in the TCGA cohort (HR 1.68; p = .036).

Beyond single gene mutations, other studies have explored the use of gene expression profiling in the prognostication of RCC. Brannon et al obtained gene expression data from 48 ccRCC samples and identified two distinct molecular subtypes, which they defined as clear cell type A and clear cell type B. Using a validation data set of 177 samples, patients with clear cell type A tumors had significantly better cancer-specific survival than those with clear cell type B tumors (median survival, 8.6 vs. 2.0 years, respectively; p = .002). This signature was subsequently validated in a meta-analysis of six ccRCC gene expression data sets encompassing a total of 480 patients. Similarly, an analysis of the TCGA data set revealed four distinct molecular subgroups, designated m1 to m4. Similar to the study by Brannon et al, postnephrectomy survival was related to these ccRCC subtypes. Interestingly, this study identified changes in key metabolic pathways within these subtypes. This included a more aggressive phenotype that was associated with increased expression of enzymes associated with the pentose phosphate shunt, glutamine transport, and fatty acid synthesis.

**Predictive Biomarkers**

As alluded to previously, the use of molecular classifications to predict response to therapy is a crucial step toward a more personalized approach to the treatment of kidney cancer. With regard to VEGF-targeted therapy, a number of tumor-specific factors have been studied as potential biomarkers, including VHL mutations and hypoxia-inducible factor levels. None of these are currently used in clinical practice and require further prospective validation. Interestingly, however, expression of the particular hypoxia-inducible factor α isoform may predict responsiveness to a new class of agents targeting hypoxia-inducible factor 2α.

Beuselinck et al performed an integrated genomic analysis of primary ccRCCs to identify subgroups that may be
more sensitive or resistant to anti-VEGF treatment. They collected primary tumor samples from 121 patients with metastatic ccRCC who were receiving first-line sunitinib. Using gene expression profiling, they identified four robust ccRCC subtypes (ccRCC1–ccRCC4). These groups showed a high correlation with the prognostic groups previously described by Brannon et al. These four molecular subtypes were associated with different responses to sunitinib treatment: ccRCC1/ccRCC4 tumors had a lower response rate ($p = .005$) and a shorter PFS and OS compared with the ccRCC2/ccRCC3 subtypes ($p = .001$ and .0003, respectively). The ccRCC4 subtype was associated with the poorest sunitinib response.

The poor-responder ccRCC1/ccRCC4 subtypes appeared to share a number of common molecular characteristics such as upregulation of MYC targets or a hypermethylated status strongly correlated with a polycomb stem-cell phenotype. The ccRCC3 tumors revealed a gene expression profile similar to that of the normal kidney and appeared to have an indolent disease course. The ccRCC4 tumors showed specific pathologic features such as a more inflammatory and sarcomatoid phenotype as well as an upregulation of cellular immune pathways. These findings suggest that the ccRCC4 subtype may be more susceptible to immune-based therapies. The authors have subsequently shown that these four molecular subtypes are also associated with outcome among patients receiving pazopanib as first-line therapy. Although intriguing, the results must be further validated in a larger, independent patient cohort before they are used in routine clinical practice for treatment selection.

There have also been a number of studies examining potential predictive biomarkers to mTOR-directed therapy. Kucejova et al identified mutations in the mTOR-negative regulator TSC1 in ccRCC and proposed that such mutations may identify tumors most likely to respond to mTOR inhibitors. Kwiatkowski et al retrospectively analyzed a cohort of 79 patients with mRCC treated with mTOR inhibitors. They performed molecular genetic analysis on both responders and nonresponders to identify mutations associated with response. Mutations in MTOR, TSC1, or TSC2 were more common for patients who experienced clinical benefit than for those who progressed. However, a substantial fraction of responders (31 of 43; 72%) had no mTOR pathway mutation identified. Thus, more research is needed before promising biomarkers such as these are used for treatment selection in clinical practice.

With regard to immune-based therapies, the use of high-dose IL-2 remains a first-line option for a select group of

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**FIGURE 1. Personalized Frontline Therapy of Renal Cell Carcinoma**

- **Metastatic/Advanced Unresectable RCC**
  - **Risk Stratification per IMDC criteria**
  - Consider PDL-1 testing

- **Favorable**
  - Consider PDL-1 testing
  - Cabozantinib*  
  - Ipi+Nivo  
  - Pazopanib

- **Intermediate**
  - Consider for High dose Interleukin-2
  - Sunitinib  
  - Cabozantinib*  
  - Ipi+Nivo  
  - Pazopanib

- **Poor Risk**
  - Treatment Options:
    - Ipi+Nivo
    - Cabozantinib
    - Pazopanib

- **PDL-1 ≥ 1%**
  - Cabozantinib*  
  - Ipi+Nivo  
  - Pazopanib

- **PDL-1 < 1%**
  - Ipi+Nivo favored  
  - Cabozantinib*  
  - Pazopanib

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Asterisks indicate that cabozantinib should be considered for patients with bone metastases. The recommendation for PDL-1 testing for treatment decisions is based on subset analysis of CheckMate 214.

Abbreviations: RCC, renal cell carcinoma; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; Ipi+Nivo, ipilimumab/nivolumab.
patients. Early evidence suggested that certain tumor characteristics such as carbonic anhydrase IX expression may predict for response. Unfortunately, the phase II SELECT trial (with 120 patients) failed to demonstrate the predictive value of carbonic anhydrase IX expression on overall response rate. The identification of reliable predictive biomarkers for immune checkpoint inhibitors is another area of active research in many tumor types, including RCC. The immune checkpoints most commonly targeted in cancer are the PD-1/PD-L1 pathway and the CTLA-4 pathway. In mRCC, the PD-1 inhibitor nivolumab has shown activity in the second-line setting, as well as in the first-line setting in combination with the CTLA-4 inhibitor, ipilimumab.

One of the most studied potential biomarkers for immunotherapy is PD-L1 expression. Unlike in other tumors, PD-L1 has not been shown to be a reliable predictor of response to anti–PD-1 therapy in RCC. In the CheckMate 025 trial exploring nivolumab in the second-line setting, a benefit was observed with nivolumab irrespective of PD-L1 expression. In a subgroup analysis of the previously discussed CheckMate 214 trial, patients with tumor PD-L1 of 1% or greater demonstrated a higher response rate and improved PFS with nivolumab and ipilimumab compared with sunitinib, but those with less than 1% expression still had a response rate of 37%. Immunohistochemistry 151 is a recently reported randomized trial that compared bevacizumab and atezolizumab therapy to sunitinib, specifically in PD-L1 positive (> 1% expression on tumor infiltrating cells; SP142 assay) patients with metastatic renal cancer. The primary endpoint of the study was investigator assessed PFS in PD-L1 positive patients with untreated metastatic RCC and OS in all patients by intent to treat. The results revealed that PFS was significantly improved with the combination in PD-L1 positive patients (HR 0.74; 95% CI, 0.57–0.96; p = .0217). Median PFS was 7.7 months with sunitinib and 11.2 months with atezolizumab and bevacizumab combination. The OS results are not mature at the time of present report. In general, there are several key limitations with the use of PD-L1 expression as a potential biomarker. These include heterogeneity between the primary and metastatic sites as well as intratumor heterogeneity. PD-L1 is also a dynamic biomarker, which may change based on prior VEGF-targeted therapy. Other limitations involve the technical methods used, including the choice of antibody, the selected cutoffs to define positivity, and the types of cells analyzed.

To explore genomic alterations in cRCC that may correlate with response to anti–PD-1 therapy, Miao et al performed whole exome sequencing of metastatic cRCC from 35 patients treated with nivolumab. In this analysis, they found that loss-of-function mutations in the PBRM1 gene appeared to be associated with increased clinical benefit to immune checkpoint therapy. Those with PBRM1 loss had significantly prolonged OS and PFS compared with patients without PBRM1 loss (log-rank p = .0074 and p = .029, respectively). These findings were confirmed in an independent validation cohort of 63 patients with cRCC treated with checkpoint inhibitors. It is speculated that PBRM1 loss may alter global expression profiles to influence responsiveness to immune-based therapies. The use of genomic analysis to predict response to immunotherapy represents an exciting step forward in the personalized care of mRCC. These findings will need further prospective validation before they are used in clinical practice.

Non–Clear Cell Renal Cell Carcinoma

CCRCC represents approximately 20% of diagnoses and comprises a number of distinct histologies, each of which appears to have unique biology. The most common of the non–clear cell variants is papillary RCC. Durinck et al performed integrated genomic analyses of 167 non–clear cell tumors, including 67 papillary RCCs. The authors identified 10 significantly mutated genes, including MET, NF2, SLCA5A3, PKNK, and CPQ. The TCGA Network recently performed a comprehensive molecular characterization of papillary RCC from 161 samples and confirmed two clinically and biologically distinct subtypes. Type I disease was noted to bear a higher frequency of alterations in the MET proto-oncogene, whereas type II tumors had CDKN2A silencing and SETD2 mutations. Data from the French RCC Network further support MET as an oncogenic driver across papillary RCC subtypes. In their analysis of 220 samples, 81% and 46% of type I and type II cases, respectively, demonstrated alterations in the MET gene.

These findings have led to interest in exploring the use of MET-directed therapies in papillary RCC. The predictive ability of MET mutational status was demonstrated in a phase II trial looking at the MET inhibitor foretinib in metastatic papillary RCC. In this trial, the presence of a germline MET mutation was highly predictive of a response to this novel targeted therapy. Another phase II study evaluated the safety and efficacy of the MET inhibitor savolitinib for patients with papillary RCC according to MET status. In this trial, ORR was significantly higher for patients with MET-driven disease (18% vs. none; p = .002). Median PFS for patients with MET-driven and MET-independent disease was 6.2 and 1.4 months, respectively (HR 0.33; p < .001). Given these findings, an international, randomized, phase II study led by the Southwest Oncology Group (SWOG 1500) is further exploring this approach. This trial is randomly assigning patients with metastatic papillary RCC to receive either sunitinib or one of three MET-directed therapies: savolitinib, cabozantinib, and crizotinib. There will be an additional exploratory evaluation of MET mutational status and expression. The results of this trial could help change the treatment paradigm of nccRCC and further promote a more personalized approach to therapy.

Future Directions: ctDNA

RCC is characterized by a high degree of intratumor heterogeneity. Analyses of RCC samples have shown that a single tumor biopsy may reveal only a minority of the genetic alterations within the entire tumor and that differences in genetic alterations are seen between the primary and metastatic sites. This degree of heterogeneity and clonal
 evolves complications of biomarker development and the delivery of precision medicine. Given these limitations, there has been increasing interest in the use of ctDNA in kidney cancer.

Pal et al\textsuperscript{66} conducted the largest patient series of ctDNA evaluation in mRCC to date. In this study, they obtained ctDNA profiles from a cohort of 220 consecutive patients with mRCC.\textsuperscript{66} Genomic alterations were detected for 79% of patients. The most frequent alterations included \textit{TP53} (35%), \textit{VHL} (23%), \textit{EGFR} (17%), \textit{NF1} (16%), and \textit{ARID1A} (12%). They also attempted to define differences in the ctDNA profile across lines of targeted therapy. When looking at post-first-line VEGF-therapy versus first-line VEGF-therapy profiles, they identified differences in genomic alterations: \textit{TP53} (64% vs. 31%; \(p = .04\)), \textit{NF1} (29% vs. 4%; \(p = .02\)), and \textit{PIK3CA} (29% vs. 8%; \(p = .07\)). These changes may suggest a selective pressure from therapy and could imply a role in resistance. Although it is not without a number of important limitations, this study illustrates the potential of ctDNA in further evaluating the genomic diversity of RCC. In the future, the use of ctDNA may expedite the selection of novel targeted therapies.

\section*{CONCLUSION}

In summary, the treatment of advanced RCC has undergone an impressive transformation over the last decade. With a number of highly effective therapies available across multiple lines, it will become increasingly important to develop a more tailored approach to treatment selection. Clinical prognostic models like the IMDC have shown a predictive ability in the context of immune checkpoint inhibition in the first-line setting and will likely be used in clinical practice for patient selection. In Figure 1, we present a proposed plan based on current available information to help determine frontline therapy of mRCC. As our understanding of the genomic landscape of RCC improves, a number of molecular markers are being explored as biomarkers. These include robust gene expression profiles that will hopefully further improve our ability to predict who will and will not respond to targeted therapy. Novel platforms such as ctDNA analysis may also provide a less-invasive avenue toward personalized medicine. In the end, given the complexity of cancer treatment, it will likely require a combination of clinical and biologic approaches to fully realize the potential of precision oncology.

\section*{References}


Systemic Therapy for Advanced Urothelial Carcinoma: Current Standards and Treatment Considerations

Brian Dietrich, MD, Arlene O. Siefker-Radtke, MD, Sandy Srinivas, MD, and Evan Y. Yu, MD

OVERVIEW

Urothelial carcinoma is the sixth most common malignancy in the United States. Although most are diagnosed with non–muscle-invasive malignancy, many patients will develop recurrent disease within 5 years, with 10% to 20% developing advanced muscle-invasive or more distant incurable disease. For such patients, clinical outcomes have remained suboptimal, although recent therapeutic advances have brought new hope to the field. Here, we discuss the main systemic treatment options available for the treatment of patients with advanced disease. This review begins with traditional chemotherapy, which remains a first-line treatment option for many patients. The second section focuses on the evolving landscape of immunotherapy, specifically on approved checkpoint inhibitors and future challenges. Last, we address advances in targeted treatments, including angiogenesis and fibroblast growth factor receptor (FGFR) inhibitors as well as antibody-drug conjugates. As the number of available treatment options continues to expand, ongoing trials to investigate the best sequence and combination strategies to incorporate these drugs into clinical practice will help delineate the future.

Bladder cancer is the sixth most common cancer in the United States, with an estimated 79,030 cases diagnosed in 2017.¹,² Men are four times more likely to develop disease than women, with approximately 60,490 men and 18,540 women diagnosed annually.¹,² Although the majority of cases are non–muscle-invasive malignancy, nearly 70% of these will have a recurrence within 5 years, with 10% to 20% developing advanced muscle-invasive or metastatic disease.³ Despite multidisciplinary therapeutic advances, clinical outcomes remain suboptimal, with 5-year survival rates around 77% for all stages combined and less than 15% for those with metastatic disease.⁴ Further, urothelial malignancies frequently occur in an older population, many with comorbidities, rendering a large percentage of newly diagnosed patients ineligible to receive standard chemotherapy regimens. Overall outcomes have been rather static for decades, with some recent improvements, yet there remains an unmet need for newer interventions. Here, we first review historic standard chemotherapy regimens, followed by more recent targeted and immunotherapy options for the management of advanced bladder cancer.

SYSTEMIC CHEMOTHERAPY IN ADVANCED UROTHELIAL CANCER

On its inception, administration of the chemotherapy agent cisplatin fostered a genuine sense of excitement in the field of urothelial cancer, generating similar excitement and hope to what we are currently seeing with immune checkpoint inhibition. However, despite the initial enthusiasm and extensive trials that followed over several decades, we found that there was a plateau in the therapeutic response and survival that could be achieved with combinatorial chemotherapy.

Methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) showed evidence of clinical activity and survival advantage compared with combination treatments.⁶ Despite several decades of research with different chemotherapy combinations, investigators have not been able to influence survival beyond the initial outcomes observed with MVAC. The major “improvement” in chemotherapy has been in decreasing toxicity, with the adoption of gemcitabine and cisplatin (GC) as the standard of care because of decreased mucositis and neutropenic fever in patients with incurable urothelial cancer.⁷

Dose-Dense Therapy

The development of dose-dense chemotherapy combinations has resulted in improved toxicity and a shorter duration of treatment compared with MVAC but has had limited impact on clinical outcomes. Sternberg et al⁸ reported decreased mucositis and neutropenic fever rates with dose-dense MVAC compared with MVAC in metastatic urothelial cancer, resulting in a resurgence of this combination as a neoadjuvant treatment of urothelial cancer. Several
neoadjuvant clinical trials have suggested similar downstaging rates with dose-dense MVAC, a shorter time to surgery,9,11 and comparable long-term survival9 as has been observed with traditional MVAC.

Dose-dense strategies have been explored with GC as well. Bellmunt et al12 reported more cycles delivered and an improved toxicity profile with a triple combination of gemcitabine, paclitaxel, and cisplatin given on a 3-week schedule compared with a 4-week schedule of GC. Dose-dense GC on a 2-week schedule has also been evaluated, although that study was closed prior to completing enrollment after finding higher rates of venous thromboembolism in the treated patients.13

GC is being used as a backbone for the addition of other novel agents, including immune checkpoint inhibitors and bevacizumab, in currently active trials. Trials with other agents did not suggest any additive benefit. Hussain et al14 reported no additional activity and increased toxicity, with higher than expected rates of thromboembolism resulting in dose reduction of the chemotherapy, in a small randomized trial of GC with or without cetuximab in a group of unselected patients with metastatic urothelial cancer. Another trial of HER2-positive patients explored the addition of trastuzumab to the combination of gemcitabine, paclitaxel, and carboplatin but could not determine additive benefit with trastuzumab and reported higher rates of cardiac toxicity.15

Combining Chemotherapy With Immunotherapy
Early attempts to incorporate immune-modulating agents with systemic chemotherapy resulted in minimal impact on clinical activity. One of the earliest trials using the immune-modulating agent α-interferon with fluorouracil and cisplatin had evidence of clinical activity but was more toxic than MVAC.16 With the recent advances in immune checkpoint inhibition, Galsky et al17 explored the combination of GC with ipilimumab. Despite the addition of ipilimumab, there did not appear to be an impact on survival greater than that observed with historical data on chemotherapy alone. Although ipilimumab did appear to affect the immune system, resulting in increased levels of circulating CD4 and CD8 T cells, the rates of immune-mediated toxicities appeared lower than what was typically observed with this dose of ipilimumab. Therefore, one might consider whether the chemotherapy may have resulted in down-modulation of the immune response. Currently, there are many clinical trials ongoing combining systemic chemotherapy with immune checkpoint inhibitors exploring the impact of these combinations in the frontline treatment of metastatic urothelial carcinoma and beyond (Table 1).

Selecting Chemotherapy: Clinical Factors
The use of cisplatin-based chemotherapy has been limited by the toxicity in patients with urothelial cancer, whose frequent comorbid conditions limit their ability to tolerate aggressive therapy. It is estimated that only a minority of patients are actually candidates for or receive a cisplatin-based chemotherapy regimen.18 As a result, many have focused on the use of clinical factors to select patients for treatment.

Poor kidney function frequently occurs in patients with urothelial carcinoma, either from direct obstruction or infiltration of urothelial tumors or the comorbid conditions commonly associated with this disease. An expert consensus statement suggested a glomerular filtration rate of greater than 60 mL/min as optimal for the use of cisplatin-based chemotherapy.19 Although this has resulted in the FDA’s threshold for adequate renal function for drug development in patients considered cisplatin eligible, it should be noted that many investigators have performed clinical trials of cisplatin-based chemotherapy in those with glomerular filtration rates as low as 50 to 55 mL/min.9,20 Such patients typically receive aggressive hydration with a full 3 L of post-cisplatin hydration and have decompression of obstructed kidneys with nephrostomy tubes to tolerate such therapy. Others have advocated for a split-dose schedule of cisplatin on days 1 and 2 for glomerular filtration rate between 50 and 60 mL/min (and even as low as 40–50 mL/min, which is the current standard at The University of Texas MD Anderson Cancer Center). Aggressive fluid hydration is essential when treating patients with these lower glomerular filtration rates.

Poor hearing and peripheral neuropathy are additional limitations for the use of a cisplatin-based regimen. A combination of ifosfamide, doxorubicin, and gemcitabine avoids these nerve-damaging effects and has shown evidence of clinical activity with downsizing rates and survival similar to what has been reported with neoadjuvant MVAC.21 However, it should be noted that this combination requires hospitalization, use of mesna, and a sodium acetate infusion,
**TABLE 1. Actively Accruing Immunotherapy Combination Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>ClinicalTrials.gov Identifier</th>
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<th>Disease State</th>
<th>Phase</th>
<th>Estimated Completion Date</th>
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*Continued*
but remains a consideration for patients younger than age 80 with a glomerular filtration rates greater than or equal to 50 mL/min.

**Selecting for Chemotherapy by Mutation Testing**

Alterations in DNA repair pathways have long been implicated in the development of urothelial cancer.22 One variant, ERCC2/XPD, has been implicated in both cisplatin sensitivity and cisplatin resistance in squamous tumors of the head and neck23 and non–small cell lung cancer,24 respectively. More recently, Van Allen et al25 reported enhanced cisplatin sensitivity for ERCC2-mutated urothelial cancer, finding that of the tumors downstaged to pT0/pTisN0 with neoadjuvant cisplatin-based chemotherapy, ERCC2 was the most consistent mutation noted in the cisplatin responsive group.

Mutations of the HER2 pathway have also been implicated in cisplatin sensitivity. Groenendijk et al26 found that ERBB2 mutations were present in nine of 38 complete responses (CRs) and none of the 33 nonresponders to neoadjuvant cisplatin-based chemotherapy. They also reported ERCC2 mutations in six of the 38 patients with a CR and two of the 33 patients whose disease did not respond to treatment, although this association did not meet statistical significance.26 Larger data sets are clearly needed to validate the role of ERBB2 and ERCC2 in predicting response to cisplatin-based chemotherapy.

**CHECKPOINT INHIBITORS FOR ADVANCED DISEASE**

The concept for using immunotherapy drugs in bladder malignancies is not novel, having now been in use since the 1960s, when immune-mediated therapeutic effects, some persisting for extended periods of time, were first demonstrated using intravesical *bacillus* Calmette-Guerin in non–muscle-invasive bladder cancer.27 FDA approval for the treatment of in situ carcinoma of the bladder and prophylaxis of recurrent tumors following transurethral resection of a bladder tumor was granted in 1990. Since that initial inception, there has been an explosion of interest in the application of novel immune therapies in treating a variety of malignancies, including bladder cancer. Bladder cancer is a heterogeneous malignancy with a high frequency of somatic mutations,28 on par with other disease processes such as melanoma and non–small cell lung cancer. This hypermutational phenotype yields an increase in neoantigen burden, which is hypothesized to correspond to a tumor’s sensitivity to immune checkpoint blockade that can be exploited by a number of therapeutic agents.29,30 Although a number of immune checkpoint proteins exist, PD-1 and its ligand counterpart PD-L1 are the most common targets of currently approved drugs. Exploitation of the pathway has revolutionized the treatment of patients with advanced disease, leading to the FDA approval of five agents since May 2016, with applications in cisplatin-ineligible patients and patients previously treated with platinum-based chemotherapy.

**Immunotherapy for Advanced or Recurrent Disease: Previously Treated Patients**

Although platinum-based chemotherapy is still used as standard frontline therapy for those eligible, progressive disease inevitably occurs. Beyond chemotherapy, many effective therapeutic options are now available, including five different checkpoint inhibitors: atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab. Atezolizumab (Tecentriq; Genentech) is a humanized, monoclonal antibody targeting PD-L1, leading to inhibition of PD-1 and B7.1 receptor interaction.31 Efficacy of the drug was demonstrated in cohort 2 of the single-arm, open-label

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**TABLE 1. Actively Accruing Immunotherapy Combination Trials (Cont’d)**

<table>
<thead>
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<th>Study</th>
<th>ClinicalTrials.gov Identifier</th>
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<td>Metastatic, second-line</td>
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Abbreviations: BSC, best supportive care; MSK, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; UC, University of California; PD, progressive disease.
phase II IMvigor 210 study, leading to accelerated approval in May 2016 on the basis of encouraging, durable response rates. To be eligible for the study, patients were required to have disease progression during or following therapy with platinum-based chemotherapy, or within 12 months of completion of neoadjuvant or adjuvant therapy. Objective response rate (ORR) by RECIST criteria was the primary endpoint of the study. PD-L1 status was prospectively analyzed using the Ventana SP142 assay by Roche, using 5% as a cutoff for high expression by immunohistochemical staining. Atezolizumab was administered as a 1,200 mg intravenous infusion given on day 1 of each 3-week cycle, continuing until disease progression or unacceptable toxicity. At 14.4-month median follow-up, the ORR was 14.8% in the 310 treated patients, including 17 CRs (5.5%). A greater ORR was seen in the high-PD-L1 group (26%), including 12 CRs in the patients with 5% or greater PD-L1 expression, although responses (including CRs) occurred even in the absence of PD-L1. Perhaps even more important, the majority of those with a treatment effect showed promising durability, with continuing responses in 38 of the 45 responders (84%) at a median follow-up of 12 months. Common side effects include fatigue, nausea, fever, decreased appetite, and possible immune-related effects, with 6.5% of patients requiring corticosteroid administration and 2.3% needing thyroid hormone supplementation.

IMvigor 211 was the larger phase III study intended to validate the results of the prior phase II study using atezolizumab for second-line therapy, with overall survival (OS) being the primary endpoint. Patients were randomly assigned to receive either atezolizumab or investigator’s choice of paclitaxel, docetaxel, or vinflunine. Confirmed objective responses were similar between the chemotherapy and atezolizumab arms, and the study disappointingly fell short of its primary endpoint of OS. Numerically longer duration of responses did occur in the atezolizumab arm. Although the treatment responses for atezolizumab were similar to those seen in the phase II study, the results in the chemotherapy arm were better than the planned study assumptions, which may factor into why the study failed to reach its primary endpoint.

Pembrolizumab (Keytruda; Merck) is a humanized antibody targeting PD-1, leading to blockade of PD-L1 and PD-L2 ligands. KEYNOTE-045 was a randomized phase III trial comparing pembrolizumab given at a dose of 200 mg every 3 weeks to investigators’ choice of either paclitaxel, docetaxel, or vinflunine. Confirmed objective responses were similar between the chemotherapy and pembrolizumab arms, with the study disappointing in its primary endpoint of OS. Numerically longer duration of responses did occur in the pembrolizumab arm. Although the treatment responses for pembrolizumab were similar to those seen in the phase II study, the results in the chemotherapy arm were better than the planned study assumptions, which may factor into why the study failed to reach its primary endpoint.

Nivolumab (Opdivo; Bristol-Myers Squibb) is a fully human IgG4 antibody that targets PD-1. The benefits of nivolumab in advanced disease have been demonstrated in two studies of patients with platinum-pretreated disease, CheckMate 032 and CheckMate 275, leading to regulatory approval of the agent in February 2017. In the phase I/II open-label CheckMate 032 study, patients were given nivolumab at a dose of 3 mg/kg intravenously every 2 weeks, with ORR as the primary endpoint. At a median follow-up time of 15.2 months, the ORR was 24.4%, with five patients (6%) achieving a CR. Responses to therapy were observed regardless of level of PD-L1 expression. Skin (seen in 42% of subjects) and gastrointestinal (10%) AEs were most commonly reported, and there were two treatment-related deaths from thrombocytopenia and pneumonitis. Checkmate 275 was the larger phase II study evaluating nivolumab in patients with locally advanced, unresectable, or metastatic disease following treatment with a platinum-based chemotherapy regimen. ORR was the primary endpoint of the study, with 19.6% of patients responding at a median follow-up of 7.0 months. Responses occurred irrespective of the level of PD-L1 expression, although this was measured for subgroup analysis using the Dako assay with cutoffs of 1% and 5%. The collective median OS was 8.7 months, with survival rates of 6.0 and 11.3 months for PD-L1 levels above and below 1%, respectively. Diarrhea and fatigue were commonly reported, with grade 3 or 4 toxicity occurring in 17.8% of patients.

The humanized PD-L1 antibody durvalumab (Imfinzi; AstaZeneca) demonstrated efficacy based on the phase I/II 1108 study of 191 patients who were pretreated with platinum-based chemotherapy. Treatment was given intravenously every 2 weeks at a dose of 10 mg/kg. ORRs occurred in 17.8% of patients, with 3.7% achieving a CR. ORRs were higher for those with high PD-L1 expression, with 27.6% of tumors with high PD-L1 expression vs. 5.1% of those with low or no expression responding. Median OS was 18.2 months (although OS data were considered immature at time of the data cutoff), with 55% of patients alive at 1 year. High-grade immune-related AEs occurred in 2.1% of cases, including two deaths from immune-related pneumonitis and hepatitis. Accelerated regulatory approval was given to durvalumab in May 2017 for second-line use. Currently, the phase III DANUBE trial is evaluating durvalumab for frontline use regardless of platinum eligibility, either as a single agent or in combination with the CTLA-4 antibody tremelimumab, compared with standard platinum-based therapy.

The last of the PD-L1 antibodies, avelumab (Bavencio; EMD Serono/Pfizer), received conditional regulatory approval.
in May 2017 for second-line treatment of urothelial carcinoma after a platinum-based regimen, on the basis of the results of a 44-patient phase IB expansion cohort. Treatment was given at a dose of 10 mg/kg intravenously every 2 weeks, with safety and tolerability being the primary endpoints. Secondary endpoints included PFS, OS, ORR by RECIST 1.1 criteria, and PD-L1 associations with response. At a median follow-up of 16.5 months, ORR was 18.2%, including CRs in 5 of the 44 patients (11.4%) and 15 patients with stable disease. Notably higher response rates occurred in the PD-L1-positive tumors (53.8% vs. 4.2%), with durable responses in the majority of cases. A 13.7-month median OS was seen in the cohort. Treatment-related AEs were similar to other immunotherapy agents, including fatigue (31.8%), nausea (11.4%), infusion reactions (20%), and immune-related toxicities (20.5%, with hypothyroidism being the most common). No treatment-related deaths occurred in this phase I cohort. Avelumab is also currently being evaluated in combination with other immunotherapy agents, including CRs in 5 of the 44 patients (11.4%) and 15 patients with stable disease. Notably higher response rates occurred in the PD-L1-positive tumors (53.8% vs. 4.2%), with durable responses in the majority of cases. A 13.7-month median OS was seen in the cohort. Treatment-related AEs were similar to other immunotherapy agents, including fatigue (31.8%), nausea (11.4%), infusion reactions (20%), and immune-related toxicities (20.5%, with hypothyroidism being the most common). No treatment-related deaths occurred in this phase I cohort. Avelumab is also currently being evaluated for use as a maintenance therapy in the phase III JAVELIN Bladder 100 study, which randomly assigns patients who do not progress after completing first-line platinum chemotherapy to a maintenance regimen of avelumab plus best supportive care versus best supportive care alone, with OS being the primary endpoint. The study is expected to be completed by 2020.

**Frontline Immunotherapy: Cisplatin-Ineligible Patients**

Of the approved immunotherapy agents, only atezolizumab (Tecentriq) and pembrolizumab (Keytruda) are approved as first-line therapy for patients ineligible to receive cisplatin chemotherapy. Use of atezolizumab in the frontline metastatic setting for cisplatin-ineligible patients was evaluated in cohort 1 of the phase II IMvigor210 study. This cohort enrolled 119 patients ineligible to receive cisplatin, most commonly because of renal dysfunction or suboptimal performance status (ECOG 2 or higher). At a follow-up time of 17.2 months, ORR was 23%, which included 9% achieving a CR. Protracted responses were seen as well, with 19 of the 27 responders having continued treatment benefit at the time of analysis. Expression of PD-L1 did not correlate with responses seen. The median OS for the group was 15.9 months. Twelve percent of patients developed serious immune-related AEs, warranting discontinuation of therapy in fewer than 10% of patients because of treatment-related effects. Atezolizumab received regulatory approval for frontline use in cisplatin-ineligible patients in April 2017 on the basis of the durable responses seen in IMvigor210.

The phase II study KEYNOTE-052 included patients with advanced disease ineligible to receive cisplatin treatment, most frequently because of renal dysfunction or poor performance status. The study enrolled an older patient population, with a median age of 74, a third of whom were older than age 80. Treatment with pembrolizumab was administered every 3 weeks for up to 2 years, with ORR as the primary study endpoint. At 9.5-month median follow-up, a 29% response rate was seen, 7% of which were CRs. Responses could be seen at all levels of PD-L1 expression, although the high-PD-L1 (≥ 10%) subgroup yielded greater results. Approximately 11% of subjects discontinued treatment because of side effects. Given the clinically meaningful, durable responses demonstrated in KEYNOTE-052, accelerated approval was granted for use in cisplatin-ineligible patients in May 2017.

**Immunotherapy: Challenges and Future Considerations**

Although the use of PD-1/PD-L1 drugs has yielded great advances, many limitations and challenges remain. The promise of immunotherapy is tempered by the low proportion of patients benefiting from the drugs, with response rates of only about 20% on average. Whether these numbers can be improved is currently being evaluated in a number of ongoing trials combining immunotherapy with radiation treatments, chemotherapy, vaccines, and other immunotherapy agents.

Selecting which patients are likely to benefit from a durable response is urgently needed. Various PD-L1 assays are currently the most readily available study, although PD-L1 is an imperfect biomarker, lacking a standardized assay for staining and accepted metrics to define expression thresholds. Furthermore, PD-L1 is not universally predictive of treatment response, with some studies such as the IMvigor211 showing lack of predictive power (the PD-L1 biomarker unexpectedly enriched responses in both the chemotherapy and atezolizumab arms, which may in part explain some of the negative results in the study). Expression is heterogeneous within primary tumors and metastases. Because most of the tested samples are from archived tissues, these may not reflect dynamic changes in expression that may develop throughout a patient’s complex treatment course.

Gene expression profiling has been used to classify molecular subtypes of urothelial cancer that differ in their prognosis and underlying biology. Early subtyping work suggested the basal subtype, which is associated with a poor prognosis, and was predictive for a survival benefit when treated with cisplatin-based chemotherapy. The p53-like/luminal 2/luminal-infiltrated subtype was associated with chemotherapy resistance. Robertson et al recently proposed a stratification of five different subtypes (luminal, luminal-papillary, luminal-infiltrated, basal/squamous, and neuronal) of bladder cancer using integrated RNA subtype classification. Luminal subtype, which constituted 35% of specimens in this study, may demonstrate a lower probability of response to neoadjuvant chemotherapy on the basis of preliminary data from Seiler et al. The luminal-infiltrated subtype may also have lower responses to neoadjuvant chemotherapy, although express the immune markers CD270 (PD-L1) and CTLA4, which may predict for better responses to immune checkpoint inhibition. When explored in the context of immunotherapy, higher responses were observed in the luminal 2 subtype with atezolizumab and the basal 1 subtype with nivolumab, with both studies suggesting
lower responses in luminal 1 tumors that appear immunologically “cold.” Further studies are needed to validate these findings.

Tumor mutational burden has also been looked at as a potential biomarker, with correlations between high mutational burden and response rates and durability in subgroup analysis of the atezolizumab IMvigor210 study, although such sequencing assays can be difficult to standardize, and the relative mutation burden may be altered over time, causing changes in the immune signature. Multiparameter immune gene expression profiling using nanostring-based gene expression signatures is another avenue of markers being investigated in other disease entities, with translation to urothelial malignancies if successful. Immune gene expression profiling offers the advantage of profiling RNA from multiple cell types and therefore may be more fully representative of the inflammatory status within the tumor microenvironment.

For the subset of patients who do respond to therapy, the optimal duration of treatment remains unknown. On the basis of clinical trial experience, the current standard of care is to continue the drug indefinitely until progression or unacceptable toxicity. Trials are currently under way to assess the importance of length of treatment. The fact that patients who have had a response with treatment stopped for toxicity continued to maintain lack of progression gives consideration that therapy might be stopped after a finite duration. In some practices, without any data available, stopping therapy in patients achieving a CR after 6 months and in those with a partial response (PR) or stable disease after a duration of 1 to 2 years seems reasonable. Retreatment is also an area of some uncertainty. Whether patients who achieved a CR benefit from retreatment remains largely unknown. A course of chemotherapy or radiation may alter the microenvironment of the tumor and possibly allow better response on retreatment, although that remains unproven.

As we gain more experience with these immunotherapy agents, the optimal sequence of therapies is also being reconsidered. With a multitude of similar agents available, it remains unclear if one is superior over another on the basis of efficacy or toxicity, and no distinction currently exists between choosing a PD-1 versus a PD-L1 agent. The current indication for PD-1/PD-L1 blockade is for metastatic disease progressing on a cisplatin-based regimen or for patients too frail or unfit to receive platinum-based therapy. There are patients, however, in whom the use of chemotherapy may be preferred over immunotherapy drugs, and identifying better biomarkers may help elucidate the optimal treatment selection for patients. Given the demonstrated benefit in advanced disease, earlier use of PD-1/PD-L1 agents in the perioperative period and non–muscle-invasive disease is also being evaluated. It is unclear if prior exposure to these agents will alter subsequent responses for drug re-challenges with recurrent disease.

Last, the cost of any therapeutic intervention needs to be considered with a treatment from which the majority of patients will not derive therapeutic benefit. The development of better biomarkers to predict response will help ensure that agents are selected more appropriately.

TARGETED THERAPIES IN ADVANCED UROTHELIAL CANCER

Although the urothelial cancer world now has immuno-oncology agents as well as cytotoxic chemotherapy, we still have much to learn and add to improve patient outcomes. Combination therapies and sequencing of agents are of great importance. However, discovering the next wave of targeted therapies is just as pivotal, as it is clear that our advancements, although impressive, still do not lead to cures for patients with metastatic disease. In this next section, we will review select targets in clinical trials for urothelial carcinoma that we view as especially promising.

Angiogenesis

VEGF and its multiple receptors have been validated targets for improving survival in multiple cancers, including colon and lung. For urothelial carcinoma, elevated levels of VEGF correlate with worse outcomes, and inhibition of this pathway has led to attenuation of tumor proliferation and invasion. Unfortunately, attempts with tyrosine kinase inhibitors of the VEGF family have not yielded convincing success with sunitinib, pazopanib, vandetanib, or cabozantinib.

Bevacizumab, a monoclonal antibody against VEGF, is still being studied. An open-label phase II trial of gemcitabine, cisplatin, and bevacizumab 15 mg/kg every 21 days reported an impressive 72% ORR; however, the primary endpoint was 50% improvement in PFS, and the observed 8.2 months were not satisfactory to achieve that goal. Median OS of 19.1 months is difficult to interpret given the nonrandomized nature of the trial. Additionally, a concerning 21% of patients suffered from venous thromboembolic events. Another open-label phase II trial by Balar et al in a cisplatin-ineligible population combined bevacizumab with gemcitabine and carboplatin. This trial resulted in an ORR of 49%, median PFS of 6.5 months, and median OS of 13.9 months. Again, 20% of patients had venous thromboembolic events. Nevertheless, the risk/benefit ratio questions surrounding bevacizumab will be answered in a first-line, randomized, and controlled phase III trial that has completed accrual with results pending (NCT00942331).

More recently, ramucirumab, a fully humanized monoclonal antibody that binds VEGF receptor 2, has shown benefit both in randomized phase II and III trials. In the randomized phase II trial, 140 patients with metastatic urothelial carcinoma, postplatinum chemotherapy, were randomly assigned 1:1:1 to receive docetaxel versus docetaxel with ramucirumab versus docetaxel with ircucumab, a monoclonal antibody targeting VEGF receptor 1. PFS, the primary endpoint, was significantly longer in the docetaxel with ramucirumab arm at a median of 5.4 months compared with 2.8 months in the docetaxel-only arm. Ircucumab did not demonstrate benefit, with a median PFS of 1.6 months. OS, a secondary endpoint, did not significantly differ between
groups. As a result, a phase III trial\(^{67}\) was launched, which randomly assigned 530 patients with inoperable or metastatic urothelial carcinoma, who progressed during or after prior platinum-based chemotherapy, to docetaxel plus ramucirumab 10 mg/kg versus docetaxel plus placebo every 21 days. The primary endpoint was again PFS and was significantly improved in the docetaxel plus ramucirumab arm over docetaxel plus placebo, with a median of 4.07 versus 2.76 months (p = .0118), respectively. There were no major grade 3 or 4 events or unexpected toxicities. OS results are pending and discussions with regulatory agencies are ongoing.

**Fibroblast Growth Factor Receptors**

The FGFR family includes four highly conserved receptor tyrosine kinases (FGFR1–4) that bind at least 18 biologically active fibroblast growth factor ligands.\(^{68}\) Downstream signaling leads to functional roles in regulation of cell proliferation, differentiation, tumorigenesis, angiogenesis, and migration.

The biology and clinical applicability of FGFR3 is the most extensively described. Activating point mutations of FGFR3 are common (approximately 86%) in low-grade and early-stage bladder tumors.\(^{69}\) However, The Cancer Genome Atlas Research Network identified only 12% of muscle-invasive bladder cancers with FGFR3 mutations.\(^{70}\) FGFR3 mutations are also very common in upper-tract urothelial tumors, especially of the ureter.\(^{71}\) In muscle-invasive bladder cancer, the presence of FGFR3 mutation is associated with a higher frequency of CDKN2A deletion, and together they may be an independent predictor of disease progression.\(^{72}\) Oncogenic FGFR3 fusion proteins are also more common in high-grade, invasive tumors.\(^{73}\) Pharmacologic inhibition of FGFR3 leads to cytostatic effects with cell cycle arrest in G1 or G0.\(^{74}\)

FGFR1 has been less intensively studied, but increased expression at both the messenger RNA and protein levels is common.\(^{75}\) Expression of FGFR1 is high in bladder cancer cell lines with a mesenchymal phenotype, suggesting a role in invasion and metastasis.\(^{76}\) On the contrary, FGFR3-high and FGFR1-low-expressing cells have an epithelial phenotype.\(^{77}\) Therefore, muscle-invasive bladder cancer may be more FGFR1-dependent, with greater effects on epithelial-mesenchymal transition and the metastatic phenotype, instead of cell proliferation.

Initial efforts to inhibit FGFRs in clinical trials were with multikinase inhibitors. Dovitinib was tested in a phase II trial\(^{78}\) of advanced patients with urothelial bladder cancer who received prior combination platinum chemotherapy, and no responses were seen in the FGFR3 mutated population, whereas only one response was seen in the wild-type population.\(^{79}\) Hence, the trial was terminated at the end of stage 1 for lack of efficacy. Similarly, a phase II trial\(^{79}\) in the *bacillus* Calmette-Guerin–unresponsive population harboring either FGFR3 mutation or overexpression was closed early with limited activity and substantial toxicity. Pazopanib has provided an exceptionally durable response for a patient known to harbor both the FGFR3 S249C-activating mutation and amplification.\(^{80}\)

Selective FGFR-targeting inhibitors may offer more promise with less nonspecific kinase-associated toxicity. However, FGFR-selective agents offer a different toxicity profile, including hyperphosphatemia, tissue calcification, and changes in nails and hair.\(^{81}\) Early results with erdafitinib (JNJ-42756493, an inhibitor of FGFR1–4) suggested durable responses in three patients with urothelial carcinoma, one with FGFR3 translocation and another with FGFR2 truncation. The tolerability of this agent has allowed for continuous dosing with up-titration on the basis of phosphorous level. In a phase I trial, BGJ398 had three of eight patients with PR and stable disease in another three patients, all with FGFR3 mutation.\(^{82}\) AZD4547 has demonstrated durable response in two of three patients, both harboring high FGFR1 and FGFR3 expression and one with an additional mutation in the ligand-binding domain of FGFR3.\(^{83}\) Meanwhile, phase I results from the Debio 1347 trial included five patient responses of 56 total patients, and one responding patient had urothelial carcinoma with FGFR3 fusion.\(^{84}\) In patients with high FGFR1–3 tumor messenger RNA levels, rogaratinib (BAY 1163877) showed the highest response rates in the bladder cancer expansion cohort, with three PRs out of eight patients.\(^{85}\) TAS-120 did not have a measurable response in eight enrolled patients with bladder cancer.\(^{86}\) The next steps in the clinical development of the above promising agents and other ongoing FGFR targeting trials are listed in Table 2.

Another strategy to target FGFR is with monoclonal antibodies. Ten patients with bladder cancer were enrolled in a phase I trial with MFGFR18775, an FGFR3-specific monoclonal antibody, and long-term stable disease was observed in five patients.\(^{87}\) B-701 is another monoclonal antibody that blocks both wild-type and activated mutant FGFR3 receptors. Early testing with B-701 was in combination with docetaxel for patients with disease progression on or after one or two lines of prior chemotherapy, excluding taxanes. A preliminary abstract\(^{88}\) reported on 17 evaluable patients, one experienced CR, two experienced PR, and a 58% disease control rate. Five patients had FGFR3 mutation, and that included the patient with CR and another with PR. Another trial of B-701 is in combination with pembrolizumab for the metastatic or inoperable postplatinum population.

**Antibody-Drug Conjugates**

Antibody-drug conjugates are characterized by a monoclonal antibody against a highly expressed cancer cell target, with a protease-cleavable linker to a cytotoxic agent. The chemotherapeutic agent is only released internally in select cells expressing the protein target after internalization of the antibody-drug conjugate and lysosomal cleavage. Bencuximab vedotin and ado-trastuzumab emtansin are examples of such agents already regulatory approved for treatment of certain lymphomas and breast cancer, respectively. In urothelial bladder cancer, a couple of recent agents have shown good efficacy using an antibody linked to microtubule-disrupting agent monomethyl auristatin E.

ASG-15ME is targeted to SLITRK6, a type I transmembrane neuronal receptor. SLITRK6 expression is identified by
immunohistochemistry in 90% of urothelial carcinomas. In a phase I trial of heavily pretreated patients with metastatic urothelial carcinoma, 1 mg/kg was identified as the maximum tolerated dose, and toxicity was predictable, with reversible ocular AEs occurring in 29.4% of patients. Among the 51 patients across all dosing levels, there were 1 CR and 17 PRs, for a 37.5% ORR. However, unique subgroups showed impressive results, with ORR of 50% at the maximum tolerated dose, 53% in checkpoint inhibitor–exposed patients, and 46% in patients with hepatic metastases.

Another antibody drug conjugate showing impressive phase I results is enfortumab vedotin, which targets Nectin-4, which is highly expressed in multiple cancers, including urothelial carcinoma. Of 68 patients with metastatic urothelial carcinoma treated, the agent was well tolerated, with grade 3 or higher hypophosphatemia occurring in 9%. Strong antitumor activity was noted, with ORR of 40% for the entire dose range (three with CR), 46% for prior checkpoint inhibitor–treated patients, and 44% for those with liver metastasis. As a result, a phase II trial (NCT03219333) has been initiated with the goal of achieving accelerated approval in the third-line metastatic setting. Additionally, a phase I trial (NCT03299545) in combination with either atezolizumab or pembrolizumab was recently launched. A randomized phase III trial is currently being designed.

**CONCLUSION**

After a long period of stagnation, treatment strategies for the management of advanced bladder cancer have started to evolve in recent years, now encompassing traditional chemotherapy, immunotherapy, and targeted options. With a multitude of newly approved agents, the treatment paradigm continues to change, with ongoing research aimed at how best to incorporate these drugs with the current well-established therapies or in new combinations with other treatment modalities at various stages of disease. Given the ongoing lack of predictive response, continued research focuses on the development of better biomarkers or molecular profiles that may optimize treatment selection for patients.

**References**


GENITOURINARY (PROSTATE) CANCER
Management of Biochemically Recurrent Prostate Cancer: Ensuring the Right Treatment of the Right Patient at the Right Time

Daniel E. Spratt, MD, Deaglan J. McHugh, Michael J. Morris, MD, and Alicia K. Morgans, MD, MPH

OVERVIEW

Biochemically recurrent prostate cancer is an increasingly common disease state, with more than 25,000 cases occurring annually in the United States. Fortunately, progress continues to be made to more effectively identify metastatic disease, optimize existing therapies, and develop new technologies and therapeutic strategies for the timing and delivery of systemic treatments to improve outcomes. This review covers three topics related to the diagnosis and treatment of men with biochemical recurrence (BCR). First, we provide an update on the state of the rapidly evolving field of molecular imaging and its place in practice. Second, we describe validated clinicopathologic methods to risk stratify patients with biochemically recurrent disease, including new gene expression classifiers, to personalize postoperative radiotherapy (RT) timing. Last, we define our approach to optimal management with systemic therapy, including identifying the patients who may benefit most and balancing the duration and timing of treatment with consideration of the effect of therapy on quality of life (QOL) and medical complications associated with treatment.

After definitive radical therapy (e.g., surgery or RT) and before the development of overt metastatic disease, an intermediate clinical disease state of prostate-specific antigen (PSA)–only recurrence or BCR exists for thousands of men each year treated previously for localized prostate cancer. This disease state is defined by a rising PSA after radical therapy without evidence of metastatic disease on CT or 99Tc bone scan. BCR can be challenging to treat because of the absence of radiographic disease to monitor response. Additionally, there is tremendous heterogeneity in the natural history of BCR, making it critical to personalize the approach to treatment.

In the United States, there has been an increase in the incidence of biochemically recurrent prostate cancer for several converging reasons. First, in 2012, the U.S. Preventive Services Task Force discouraged the use of PSA screening for prostate cancer, leading to a reduction in PSA screening and an increase in the number of men diagnosed with high-risk localized disease. In addition, practice patterns have shifted to include an increase in radical prostatectomy (RP) for the treatment of high-risk localized disease. However, there remains a less than 10% utilization rate of adjuvant RT in eligible men, despite evidence demonstrating a survival advantage in select high-risk patients and support for adjuvant RT from the American Urological Association, the American Society for Radiation Oncology, and ASCO.

Given that 50% to 95% of men with high-risk prostate cancer will experience recurrence after localized treatment, an estimated 25,000 men will develop BCR annually in the United States.

Numerous advances are expected to lead to improvements in outcomes for the growing population of men with BCR. Novel molecular imaging techniques are providing investigators and clinicians with an improved understanding of the location and burden of the PSA-producing recurrent disease using several distinct methods, including choline, fluciclovine, and prostate-specific membrane antigen (PSMA) PET approaches. Additionally, recently developed genomic biomarkers can improve the risk stratification of patients to more accurately direct the use and timing of adjuvant or salvage RT. Finally, ongoing efforts continue to investigate the use, timing, and intensity of androgen-deprivation therapy (ADT) administration for these patients. This review addresses these recent advances and focuses principally on level one data available for men who have experienced BCR post-prostatectomy although many of the concepts may apply also to men who have recurred after definitive RT.
TABLE 1. PET Tracer Molecules and Current Clinical Use Options for Each

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Target</th>
<th>Context of Use/Indication</th>
<th>Regulatory Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDG</td>
<td>Glucose metabolism</td>
<td>Response assessment in advanced disease, especially mCRPC</td>
<td>FDA approved; CMS will reimburse for determination of treatment effects in advanced disease (as of June 11, 2013)</td>
</tr>
<tr>
<td>¹¹C-choline</td>
<td>Lipid synthesis</td>
<td>Suspected prostate cancer recurrence and noninformative bone scintigraphy, CT or MRI</td>
<td>FDA approved, September 12, 2012</td>
</tr>
<tr>
<td>Fluciclovine</td>
<td>Amino acid transport</td>
<td>Suspected prostate cancer recurrence based on elevated PSA levels following prior treatment</td>
<td>FDA approved, May 27, 2016</td>
</tr>
<tr>
<td>⁶⁸Ga-PSMA (HBED-CC; 11)</td>
<td>PSMA</td>
<td>Multiple, all investigational</td>
<td>Not approved in United States, available throughout the world in trials and off, depending on the country</td>
</tr>
<tr>
<td>¹⁸F-PyL</td>
<td>PSMA</td>
<td>Multiple, all investigational</td>
<td>Not approved in United States, available throughout the world in trials and off, depending on the country</td>
</tr>
<tr>
<td>FDHT</td>
<td>AR</td>
<td>Disease detection, prognostic, PD effects in new drug development</td>
<td>Investigational; available in United States, Europe, and Australia in trials</td>
</tr>
</tbody>
</table>

Abbreviations: FDG, fluorodeoxyglucose; mCRPC, metastatic castration-resistant prostate cancer; FDA, U.S. Food and Drug Administration; CMS, Centers for Medicare and Medicaid Services; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; FDHT, fluoroxyhydrotestosterone; AR, androgen receptor; PD, pharmacodynamic.

IMAGING STRATEGIES IN BIOCHEMICAL RECURRENCE
Radiographic detection of prostate cancer in the context of BCR is essential to define disease distribution, plan treatment, and set expectations. Distinguishing between a local recurrence and metastases is critical to determine whether treatment will entail local salvage therapy to eradicate disease, further surveillance, or systemic treatment to control disease progression. Radiographic detection of disease is contingent on the performance characteristics of the imaging technology that is used. Clinicians and patients relying on conventional cross-sectional imaging or bone scintigraphy have been hampered by the limits of early disease detection, especially when PSA values are low. This limitation has led to an enthusiastic investigation and adoption of newer molecular imaging modalities, including ¹¹C-choline, ¹⁸F-fluorocholine, ¹¹C-acetate, fluciclovine, and ⁶⁸Ga- and ¹⁸F-radiolabeled PSMA-directed agents, which typically detect disease earlier than standard imaging techniques (Table 1).

Choline is a participant in cell membrane and lipid biosynthesis. It has been used for molecular imaging and for the detection of occult disease since the late 1990s. In a retrospective analysis of 358 patients with BCR after RP, the tracer demonstrated sensitivity of 85%, specificity of 93%, positive predictive value of 91%, negative predictive value of 87%, and overall accuracy of 89%. On multivariate analysis, old age, PSA level, prior biochemical failure, and pathologic staging and positive nodal involvement were all highly associated with a higher likelihood of a positive finding on the scan. Receiver operating characteristic analysis showed that patients with PET/CT-positive and PET/CT-negative disease were best distinguished with a PSA cutoff of 1.4 ng/mL. However, in the range of when most salvage RT might be performed, when the PSA is less than 0.4 ng/mL, detection of disease occurs in only 21% of cases, which can limit the practical application of ¹¹C-choline PET/CT when applied in the context of routine practice.

PSA doubling time (PSA DT) was inversely related to ¹¹C-choline PET/CT positivity in patients with BCR after RP. A retrospective analysis of 170 patients reported that the percentage of patients with positive ¹¹C-choline PET/CT was 27% for PSA DT greater than 6 months, 61% for PSA DT between 3 and 6 months, and 81% for PSA DT less than 3 months. ¹¹C-choline PET/CT is U.S. Food and Drug Administration approved for patients with suspected prostate cancer recurrence and noninformative bone scintigraphy, CT, or MRI.

Fluciclovine, or FACBC, is an analog of -leucine that illuminates cells that have active amino acid transport. Like ¹¹C-choline, it has U.S. regulatory approval for men with suspected prostate cancer recurrence on the basis of...
elevated PSA levels after prior treatment. In a comparison of \(^{11}C\)-choline and fluciclovine, 100 patients with BCR after RP underwent dual \(^{11}C\)-choline and fluciclovine imaging. Fluciclovine and choline were compared head to head by patient and site of disease for 89 participants. Fluciclovine appeared to demonstrate superior performance characteristics, as it had greater sensitivity (37% vs. 32%) and specificity (67% vs. 40%). Fluciclovine also detected metastatic disease at PSA levels less than 1 ng/mL (21% vs. 14%, \(p = .0001\)), providing a method to identify local recurrence when outcomes from salvage RT may be optimized.

One of the most promising molecular imaging techniques for disease detection uses PSMA, a unique membrane-bound glycoprotein that is overexpressed on prostate cancer cells. PSMA-binding ligands are bound to the extracellular domain of PSMA. \(^{68}Ga\)-PSMA-HBED-CC (\(^{68}Ga\)-PSMA) is a small-molecule radiotracer targeting PSMA with superior performance characteristics for disease detection in initial studies, especially at very low PSA levels. Verburg et al\(^{16}\) retrospectively studied 155 patients with biochemically recurrent prostate cancer who underwent \(^{68}Ga\)-PSMA PET/CT after primary surgery or RT. Imaging was positive in 44%, 79%, and 89% of patients with PSA levels of less than 1, 1 to 2, and greater than 2 ng/mL, respectively. In multivariate analyses, both absolute PSA and PSA DT were independent determinants of scan positivity and presence of extrapelvic lymph node metastases. This analysis included patients who had undergone surgery or RT (with or without ADT) in both the primary and salvage settings.

In another retrospective study, Eiber et al\(^{17}\) examined the use of \(^{68}Ga\)-PSMA PET/CT in 248 patients with BCR after RP. In this analysis, lesion detection rates were 97%, 93%, 73%, and 58% for PSA levels of less than or equal to 2, 1 to less than 2, 0.5 to less than 1, and 0.2 to less than 0.5 ng/mL, respectively. Detection rates were higher in patients with Gleason scores greater than or equal to 8 versus less than or equal to 7, possibly reflecting earlier findings correlating PSMA expression with Gleason score.\(^{18}\)

Although direct comparative data are limited, PSMA imaging has superior sensitivity compared with choline. In one study, 139 men with BCR underwent \(^{18}F\)-choline and \(^{68}Ga\) PET imaging.\(^{19}\) Disease detection rates were 74.4% for choline imaging alone and 85.6% when both scans were performed. Disease was detected only by the PSMA scan in 28.6% of men with PSA levels of 0.2 to 1 ng/mL, in 45.5% at PSA levels of 1 to 2 ng/mL, and in 71.4% at PSA levels of greater than 2 ng/mL. A single retrospective study compared the diagnostic accuracy of choline PET/CT with \(^{68}Ga\)-PSMA PET/CT, on the basis of histopathologic findings after sentinel lymph node dissection in patients with BCR.\(^{20}\) Preoperative imaging demonstrated that 30 of 38 (79%) and 23 of 28 (82%) patients had at least one focus of disease confirmed histologically at salvage node dissection for \(^{18}F\)-choline and \(^{68}Ga\)-PSMA PET/CT imaging, respectively. For \(^{18}F\)-choline and for \(^{68}Ga\)-PSMA, sensitivity was 71% and 87%, respectively. Specificity was 87% and 93%, respectively, positive predictive value was 67% and 76%, respectively, and negative predictive value was 89% and 97%, respectively. However, ligand-specific challenges for \(^{68}Ga\)-PSMA PET imaging exist and include difficulty evaluating tumor foci in close proximity to the bladder secondary to urinary excretion of \(^{68}Ga\)-PSMA. Further, the availability of the radionuclide is limited by generator capacity, and the short half-life (68 minutes) of \(^{68}Ga\) precludes delivery to distant PET centers.\(^{21}\) Finally, as with any PSMA-directed imaging modality, non–PSMA-producing prostate cancers, such as those that are poorly differentiated or have a neuroendocrine component, may not be assessed well with this modality.\(^{22}\)

\(^{18}F\)-DCFPyL is a novel, second-generation low–molecular weight PSMA imaging agent that offers potential advantages over the \(^{68}Ga\)-PSMA ligand.\(^{23}\) Because of the lower positron emission energy, the distance to decelerate the positron in human tissue is much shorter in comparison with \(^{68}Ga\)-PSMA, resulting in a higher image resolution. Furthermore, production volume and a longer half-life offer practical advantages over \(^{68}Ga\). In 14 selected patients with BCR, \(^{18}F\)-DCFPyL PET/CT was performed in addition to \(^{68}Ga\)-PSMA PET/CT, with \(^{18}F\)-DCFPyL detecting all suspicious lesions seen on \(^{68}Ga\), with additional lesions seen in three patients on \(^{18}F\)-DCFPyL imaging.\(^{24}\) The mean maximum standardized uptake value in the concordant \(^{18}F\)-DCFPyL PSMA–positive lesions was significantly higher compared with \(^{68}Ga\)-PSMA-HBED-CC (14.5 vs. 12.2, \(p = .028\), 15 patients). The mean tumor-to-background ratios (15 patients) were significantly higher for \(^{18}F\)-DCFPyL compared with \(^{68}Ga\)-PSMA-HBED-CC using kidney, spleen, or parotid as the reference organ.

The same group examined 191 consecutive patients with BCR after RP (106 patients) and RT (85 patients) using \(^{18}F\)-DCFPyL (62 patients) or \(^{68}Ga\)-PSMA (129 patients).\(^{25}\) For a PSA of 0.5 to 3.5 ng/mL in the RP group, PSA-stratified sensitivity was 88% (15 of 17) for \(^{18}F\)-DCFPyL and 66% (23 of 35) for \(^{68}Ga\)-PSMA. This significant difference was preserved in the Gleason matched-pair analysis. Outside of this range, sensitivity was comparably low (PSA < 0.5 ng/mL) or high (PSA > 3.5 ng/mL). Tracer sensitivity in the RT group was largely PSA independent. In an orthogonal validation of 25 patients, although the direct comparison of both tracers used sequentially demonstrated excellent concordance in distribution, in 36% of patients with PSMA-positive disease, additional lesions were detected on the \(^{18}F\)-DCFPyL scan (\(p = .037\)).

**PRECISION RISK STRATIFICATION METHODS**

Merely having a BCR after prostatectomy should not trigger all men to receive salvage treatment. Decision-making should be grounded in understanding each patient’s individual prognosis and should be based on personal clinical, pathologic, radiographic, and genomic characteristics.\(^{6}\) The concept of risk stratification for men is important for identifying not only which men should receive salvage RT but also when the addition of ADT will be beneficial.
Life Expectancy Estimation
Before discussing methods to risk stratify men with biochemically recurrent disease after prostatectomy, it is imperative to understand that at no point should the treatment be worse than the disease itself. A balance should be struck between the goals of cure and preservation of QOL. An understanding of a patient’s performance status, comorbidities, and, ultimately, life expectancy is requisite to compare and contrast the benefits and harms further therapy may provide. Social Security tables and calculators leveraging data from the National Institutes of Health are available online to estimate a patient’s life expectancy to better understand a patient’s non-prostate cancer risk for death.26,27 This can then be balanced with the patient’s risk for progression, metastases, and death from prostate cancer.

Prostate Cancer Risk Stratification
Multiple risk stratification tools have been developed to capture a patient’s risk of recurrence after prostatectomy.28,29 Recently updated, the Stephenson nomogram is one of the most used and comprehensive measures that can prognosticate a patient’s risk for subsequent biochemical failure or development of distant metastases after undergoing salvage RT.29 A user-friendly method to calculate a patient’s progression-free survival using the Stephenson nomogram is available online through the Memorial Sloan Kettering website.28,30 The Stephenson nomogram includes common clinical and pathologic variables, such as surgical Gleason score (now commonly referred to as grade groups), extracapsular extension, seminal vesicle invasion, surgical margin status, and pre-RT PSA. The two variables that most influence a patient’s risk for recurrence are pre-RT PSA and the Gleason score. However, one important variable that was not captured in the updated Stephenson nomogram is PSA DT. PSA DT, often split as a PSA DT greater or less than 10 months, provides valuable prognostic information to complement other clinicopathologic variables.1 PSA DT can also be readily calculated online through the Memorial Sloan Kettering website.31

Beyond routine clinical and pathologic variables, gene expression classifiers have demonstrated the ability to further improve risk stratification.32,33 Decipher, a 22-gene expression classifier, can be run on tissue taken from the time of pretreatment biopsy or from the RP specimen. A recent individual patient–level meta-analysis of studies using the Decipher platform demonstrated that the Decipher test independently added prognostic value over the variables found in the Stephenson nomogram to predict a patient’s risk for distant metastasis.34 Furthermore, this study demonstrated that the Decipher test performed equally well in men undergoing salvage RT, suggesting that this commercially available biomarker may help with risk stratification in men with biochemically recurrent disease post-prostatectomy.

Application of Risk Stratification to Guide Treatment
Salvage radiation therapy use and timing. Leveraging all of the available risk stratification tools, including an estimate of an individual’s risk for non–prostate cancer death, will assist with making an informed decision of the timing and suitability of salvage RT for a patient with BCR. In general, men with a less than 5-year life expectancy are unlikely to benefit from salvage RT given that the median time to develop distant metastasis after PSA recurrence, without any treatment, is approximately 8 years.2 Additionally, men with an indolent recurrence (long PSA DT, low risk for distant metastasis calculated by the Stephenson nomogram, and/or a low-risk Decipher score) may not benefit from salvage RT if their life expectancy is less than 10 years. For men with a greater than 10-year life expectancy, which is the vast majority of men with BCR, the focus should be on delivering “early” salvage RT (delivered when PSA is < 0.5 ng/mL), and potentially “very early” salvage RT (PSA < 0.2 ng/mL).29,35 International guidelines recommend the use of early salvage RT, as late salvage RT (PSA > 0.5 ng/mL) consistently has demonstrated inferior survival outcomes.29,35,36 Because of this, all ongoing phase III randomized controlled trials comparing adjuvant with salvage RT have enforced early salvage RT as the experimental arm (Radiotherapy and Androgen Deprivation in Combination After Local Surgery [RADICALS; NCT00541047], Radiotherapy Adjuvant Versus Early Salvage [RAVES; NCT00860652], and GETUG-17 [NCT00667069]).

Addition of androgen-deprivation therapy to salvage radiotherapy. Recently, two randomized phase III trials of salvage RT with or without androgen pathway inhibition have reported their results.37,38 These trials have generated numerous questions given their discordant results, which are likely rooted in the differences in the cohorts themselves, treatment arms, and follow-up duration. RTOG 9601 tested the addition of 2 years of bicalutamide monotherapy to salvage RT.37 The trial had a median follow-up period of 13 years, and the patients enrolled were high risk by modern standards (67% had T3 disease, 75% had positive margins, 12% had persistently elevated PSAs > 0.5 ng/mL after prostatectomy). Furthermore, RT was delivered primarily as late salvage RT, in that only 10% of men had salvage RT when PSA was 0.2 to 0.3 ng/mL, 25% had PSA levels greater than 1.0 ng/mL, and the median PSA level was 0.6 ng/mL. Bicalutamide was associated with a reduction in distant metastasis and improvement in overall survival. However, the benefit on subset analysis was limited to men who underwent late salvage RT with PSA levels greater than 0.7 ng/mL.

The GETUG-AFU-16 trial tested the addition of 6 months of a luteinizing hormone–releasing hormone agonist to salvage RT.38 This study had a median follow-up period of 5.3 years, and patients were more analogous to contemporary treated patients (46% had T3 disease, 51% had positive margins, and the trial did not permit persistently elevated PSA levels after prostatectomy). Overall the cohort was lower risk than men enrolled in RTOG 9601. Furthermore, 75% of patients on the trial underwent early salvage RT, and only 10% of patients underwent salvage RT at PSA levels greater than 1.0 ng/mL. In this more favorable-risk population undergoing early salvage RT, the investigators did not find a significant difference between arms with regard to distant
metastasis or overall survival. They did report an improvement in biochemical control from the addition of ADT, which would be expected to be improved in patients receiving PSA-lowering therapy and is of unclear clinical significance. However, similar to RTOG 9601, they did demonstrate that men with PSA levels greater than 0.5 ng/mL appeared to derive the greatest benefit from the addition of ADT. Similar findings have been recently reported from retrospective studies demonstrating that only men with a high risk for recurrence appear to derive a benefit from the addition of ADT to salvage RT.

So what can one conclude from these two very different trials? Despite the numerous differences between RTOG 9601 and GETUG-AFU-16, it is clear that men undergoing late salvage RT (PSA > 0.7 ng/mL) with high-risk features (Gleason score 8–10, T3 disease, and/or positive margins) appear to derive a metastasis and survival benefit from the addition of long-term hormonal therapy on the basis of RTOG 9601.37 Furthermore, men who undergo early salvage RT have yet to demonstrate clinically meaningful benefits with regard to reductions in metastasis or death from prostate cancer from the addition of androgen pathway inhibition. A recent framework from a panel of multidisciplinary experts based on the available evidence can be used to help personalize the use of ADT for men receiving salvage RT and recommends omission of ADT for men undergoing early salvage RT.40 The culmination of the data has inspired a recently approved phase II randomized NRG Oncology cooperative group trial, NRG GU-006, to investigate if men undergoing primarily early salvage RT will benefit from enhanced antiandrogen therapy (apalutamide, a second-generation antiandrogen) versus placebo.

Beyond Risk Stratification

All of the risk stratification tools discussed thus far are “prognostic” biomarkers. They provide prognostic information regardless of whether the patient is treated with RT, ADT, or both. In contrast, ideally we would use “predictive” biomarkers to personalize therapy. Predictive biomarkers specifically provide information regarding how a patient will respond to a particular treatment and only that treatment. For example, estrogen receptor expression in breast cancer is a predictive biomarker for which patients will derive benefit from endocrine therapy. Women without estrogen receptor expression will not benefit from endocrine therapy. Ideally, predictive biomarkers could be used to guide the use of RT and ADT. Unfortunately, to date, there is not a single prospectively validated predictive biomarker in localized or recurrent prostate cancer, but multiple strategies are being developed and investigated.41,42 One promising predictive biomarker to guide the use of ADT has been created on the basis of the PAM50 molecular classifier that was developed for breast cancer.41 This classifier divides patients into luminal and basal subtypes and has been shown to predict which patients will derive benefit from addition of ADT. To validate this work, the previously mentioned NRG GU-006 randomized phase II placebo-controlled trial will be stratifying patients by their PAM50 subtype to prospectively validate if this biomarker can predict which men undergoing salvage RT will benefit from apalutamide.

INITIAL SYSTEMIC THERAPY FOR BIOCHEMICAL RECURRENCE: OPTIMIZING TIMING OF THERAPY AND PATIENT SELECTION

ADT remains the backbone of systemic therapy for the treatment of men with BCR of prostate cancer who are not candidates for local salvage therapy or who have BCR after salvage treatment. Exposure to ADT will eventually lead to the development of castration-resistant disease if continued for long enough, and the benefit of treatment in the biochemical recurrent setting has not been clearly defined. Evidence defining the optimal timing and duration of ADT in the setting of BCR is lacking. In contrast, the complications associated with systemic therapy are better defined and are a critical aspect of treatment decision-making in this setting. A thoughtful discussion of the risks and benefits of treatment and its timing are essential for decision-making for men with BCR.

Complications of Androgen-Deprivation Therapy

Although treatment with ADT is considered relatively tolerable for a majority of men, treatment is not without complications. In addition to those that immediately and noticeably impair QOL, such as hot flashes, loss of interest in sexual activity, erectile dysfunction, and psychological and cognitive effects, ADT also increases the risk for medical complications that can cause morbidity and increase mortality in this predominantly elderly patient population.43 Medical complications, including the development of osteoporosis, diabetes, sarcopenia, and cardiovascular disease, occur at higher rates in men treated with ADT compared with untreated men.44-46 It is critical to consider the risk for these complications in addition to potential benefits when discussing treatment options with men experiencing BCR.

Timing of Systemic Therapy: Early Versus Late

As described above, one of the challenges in managing BCR of prostate cancer is defining the disease state and determining whether a patient meets criteria for salvage therapy locally. For men who are not receiving salvage local therapy or have BCR after salvage treatment, the next step in management is defining the optimal timing of systemic therapy. This decision is complicated by the need to balance the efficacy of the therapy, preferably measured by improvement in overall and disease-specific survival, against minimization of side effects and decline in QOL in this generally asymptomatic population.

Two observational studies attempted to determine whether earlier or later initiation of treatment is superior.40,51 In the first, 2,096 men in the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) database were identified as experiencing biochemical relapse after initial treatment with RT or prostatectomy. The investigators assessed the effect of immediate (initiated ADT within 3 months of
PSA relapse) versus deferred ADT (initiated ADT at development of metastases or 2 or more years after PSA relapse) on overall and prostate cancer–specific survival using complex mathematical modeling. The hazard ratio (HR) for mortality comparing immediate to deferred ADT was 0.91 (95% CI, 0.52–1.60), demonstrating no significant advantage to early initiation of ADT in this setting. There were too few prostate cancer–related deaths to assess the association with prostate cancer–specific mortality. A separate investigation of the optimal timing of ADT for men with BCR was a retrospective cohort study of 5,804 men with BCR after RT or prostatectomy identified from three managed care systems. The investigators assessed survival associated with early initiation of ADT in the setting. There were too few prostate cancer–related deaths to assess the association with prostate cancer–specific mortality. A subgroup analysis of men with PSA DT less than 9 months found an association between improved overall and prostate cancer–specific survival and treatment with ADT in both the prostatectomy and RT treated groups (overall survival and prostate cancer–specific mortality HRs, 0.35 [95% CI, 0.20–0.63] and 0.43 [95% CI, 0.21–0.91] for the prostatectomy-treated cohort and 0.62 [95% CI, 0.48–0.80] and 0.65 [95% CI, 0.47–0.90] for the RT cohort). These results should be interpreted in the context of the limitations of a retrospective claims-based analysis but raise questions regarding potential benefit of earlier treatment with ADT in subsets of men at high risk for progressive disease. A recently reported prospective randomized phase III trial sought to evaluate the effect of timing of initiation of ADT in men with BCR after RT or prostatectomy. The TOAD study (TROG 03.06 and VCOG PR 01-03) randomly assigned 261 of a planned 750 men with BCR to receive immediate (initiated ADT within 8 weeks of randomization) or delayed (initiated ADT 2 or more years after randomization unless symptoms, development of metastatic disease, or PSA DT ≤ 6 months) ADT. The analysis was stratified by initial treatment (RT or prostatectomy), PSA DT, relapse-free interval, and plan for continuous ADT versus intermittent ADT (iADT), and men with PSA DT less than 3 months were excluded from the study. Although the study did not meet planned accrual and was halted early, the investigators found a statistically significant improvement in survival associated with early initiation of ADT when compared with delayed ADT in an unadjusted analysis (HR 0.55; 95% CI, 0.30–1.00; p = .050). However, the small sample size and borderline significance of this unadjusted analysis make it impossible to draw definitive conclusions from these findings. A QOL assessment accompanying this study demonstrated inferior QOL in the immediate treatment arm related to sexual activity and hormone treatment–related symptoms at 6 and 12 months compared with delayed therapy, though there may be less difference between groups at later time points. Given the lack of more definitive data, many clinicians attempt to balance the risks and benefits of initiating systemic therapy by opting to initiate treatment earlier in populations at high risk for rapidly developing complications from progressive prostate cancer and delay therapy in men with less aggressive recurrence. In addition to the data presented above from a retrospective cohort study assessing subgroups that may benefit from earlier ADT, there have been separate studies defining the natural history of prostate cancer recurrence and progression that identify characteristics of patients at highest risk for developing metastasis and death following prostatectomy. In one series, 1,997 men were followed for a mean of 5.3 years after prostatectomy. Overall, 315 (15%) developed PSA-only recurrence, and 103 (34%) of the men not treated with immediate systemic therapy developed metastatic disease by the conclusion of the study. Characteristics associated with more rapid metastasis and death in the cohort included a Gleason score of 8 or higher, PSA recurrence within 2 years after prostatectomy, and PSA DT less than 10 months. Although this was defined in a population that is unlikely to have received salvage local therapy, as would occur today, these data suggest characteristics of patients at heightened risk for metastasis and death after PSA recurrence in the overall population of men with BCR after prostatectomy. Whether these men would achieve benefit from systemic treatment specifically remains unknown.

Optimal Administration of Systemic Therapy

In addition to questions of timing, the optimal formulation and duration of ADT have not been defined for men with BCR. At present there are no randomized studies that directly compare the effects of surgical castration or gonadotropin-releasing hormone agonist or antagonist therapy with androgen receptor–directed therapies or combined androgen blockade in the BCR setting. The EMBARK trial is an industry-sponsored study that attempts to address this issue by randomly assigning men with high-risk BCR (defined by PSA DT less than or equal to 9 months) to receive treatment with leuprolide plus enzalutamide versus enzalutamide alone versus leuprolide alone (NCT02319837). This study does not address the question of whether earlier ADT is better than delayed treatment but does define a treatment strategy for the population of men with short PSA DT who appear to benefit from earlier initiation of ADT in the nonrandomized studies described previously. Whether treatment should be continuous or intermittent for men with BCR is also somewhat controversial. The largest study addressing this issue was an international multicenter phase III study randomly assigning 1,386 men with BCR after RT treatment to receive iADT or continuous ADT to evaluate the association between treatment and overall survival. iADT was defined as treatment with ADT for 8 months followed by cessation of treatment until the PSA rose to greater than 10 ng/mL. The study was designed as a noninferiority study, with the upper bound of the HR set at less than 1.25. After nearly 7 years of follow-up, iADT was noninferior to continuous ADT (HR 1.02; 95% CI, 0.86–1.21). In the associated QOL assessment, it was notable that only 35% of men in the iADT group recovered...
testosterone to pretreatment levels by 2 years, and only 29% of men who were potent at baseline regained potency. QOL was significantly superior in the iADT group compared with the continuous ADT group for all hormone-associated outcomes, including desire for sexual activity (p < .001) and hot flashes (p < .001). The median duration of treatment in the continuous ADT group was 43.9 months versus 15.9 months for men treated with iADT, with a median off-treatment time of 37.6 months. Given the lack of clear survival advantage associated with continuous ADT, the slightly superior QOL associated with iADT, and the duration spent off treatment, iADT is the preferred management strategy for many clinicians treating men with BCR.

CONCLUSION

Ultimately, there are many uncertain aspects of the management of men with BCR of prostate cancer, including optimal imaging approaches, risk stratification techniques, and choices regarding treatment. Ongoing studies assessing the optimal workup and treatment of men with hormone-sensitive BCR are expected to clarify some of the controversy in the next few years.

References


Prostate cancer accounts for one in every five cancer diagnoses, making it the most common cancer in men, and metastatic prostate cancer is the second most common cause of cancer-related deaths in men in the United States.\(^1\) The incidence of prostate cancer began to decline in 2000, and it has more rapidly declined since the U.S. Preventive Services Task Force changed its recommendations for prostate-specific antigen (PSA) screening in 2008 and 2011.\(^1,2\) However, over the same period in the United States, the incidence of metastatic prostate cancer is increasing, with at least one study showing a 72% higher incidence of mCSPC cases in 2013 than in 2004.\(^3,4\) Whether the increase in mCSPC is specifically related to changes in screening recommendations is unknown; however, this increase is concerning because mCSPC is generally considered to be incurable. Although localized prostate cancer has a 5-year survival rate of 100%, mCSPC has a 5-year survival rate of 29.8%.\(^5\)

The treatment landscape for metastatic castration-sensitive prostate cancer (mCSPC) has rapidly evolved over the past 5 years. Although androgen-deprivation therapy (ADT) is still the backbone of treatment, the addition of docetaxel or abiraterone acetate has improved outcomes for patients with mCSPC and become standard of care. With multiple treatment options available for patients with mCSPC, treatment selection to optimize patient outcomes has become increasingly difficult. Here, we review the clinical trials involving ADT plus docetaxel or abiraterone and provide clinicians with guidelines for treatment. Although surgery and/or radiation are standard of care for localized, intermediate- and high-risk prostate cancer, these treatments are not routinely used as part of initial treatment plans for patients with de novo mCSPC. Recent clinical data are challenging that dogma, and we review the literature on the addition of surgery and radiation to systemic therapy for mCSPC. Finally, the standard of care for oligometastatic prostate cancer (a subset of mCSPC with limited metastases) has not been established compared with that for some other cancers. We discuss the recent studies on metastasis-directed therapy for treatment of oligometastatic prostate cancer.
the available data, we discuss considerations for selection of the optimal treatment regimen for individual patients with mCSPC. Finally, we review the role for addition of surgery and/or radiotherapy to systemic therapy in de novo mCSPC and multimodality therapy for oligometastatic prostate cancer.

Evolving Treatment Paradigm of Metastatic Castration-Sensitive Prostate Cancer

Androgen-Deprivation Therapy

In mCSPC, prostate cancer cells need high levels of androgens to drive cancer growth. Accordingly, approximately 90% of patients with mCSPC will respond to initial treatment with ADT. ADT for mCSPC works by decreasing testicular production of androgens. There are multiple mechanisms of action to block testicular production of androgens, including orchietomy, luteinizing hormone–releasing hormone (LHRH) agonists to prevent luteinizing hormone secretion, and LHRH antagonists to decrease luteinizing hormone secretion. Two LHRH agonists, leuprolide and goserelin, are approved in the United States, whereas degarelix is the only LHRH antagonist approved there. The first-generation androgen antagonists flutamide, nilutamide, and bicalutamide are not recommended as monotherapy for mCSPC; however, they are frequently used when LHRH agonists are initiated to prevent testosterone flare. Until 2015, combined androgen blockade with an LHRH agonist and a first-generation androgen was commonly used to treat mCSPC. Combined androgen blockade with first-generation androgen antagonists can be considered, but data supporting the benefits are small. Furthermore, second-generation androgen receptor (AR) antagonists or androgen synthesis inhibitors may negate the observed benefits (Fig. 1).

Recent investigations have studied the optimal dosing schedule of ADT to balance efficacy with patient quality of life. In a phase III clinical trial of 3,040 men with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC), SWOG studied whether intermittent ADT is noninferior to continuous ADT. All patients were initially treated with 7 months of continuous ADT then randomly assigned to continuous or intermittent ADT if they had an ongoing PSA response. The coprimary endpoints for SWOG 9346 were noninferiority of intermittent ADT with respect to OS and quality of life 3 months after randomization. Unsurprisingly, intermittent ADT was associated with improved quality of life 3 months after randomization but not later because of the variable period of time “off therapy.” However, intermittent ADT was not found to be noninferior to continuous ADT with respect to OS (5.8 years vs. 5.1 years; hazard ratio [HR], 1.10; 95% CI, 0.99–1.23) but rather the result was inconclusive. However, SWOG 9346 raised concerns about intermittent ADT, thus perpetuating continuous ADT as the favored therapy for mCSPC.

Analyses of several clinical trials have suggested that more aggressive up-front treatment could translate to improved outcomes for patients with mCSPC. In a subgroup analysis of 1,345 patients from SWOG 9346, lower PSA values after 7 months of continuous ADT were predictive of improved median OS. Specifically, the 383 (25%) patients with a PSA greater than 4 ng/mL had a median OS of 13 months, whereas the 602 (45%) patients with a PSA less than 0.2 ng/mL had a median OS of 75 months. A follow-up analysis from the PR-7 trial, in men with biochemically recurrent prostate cancer, found that lower testosterone levels were predictive of improved cancer-specific survival and time to castration-resistant prostate cancer (CRPC). These studies suggested that deeper androgen blockade could improve clinical outcomes for patients with mCSPC.

PRACTICAL APPLICATIONS

- ADT plus docetaxel for six cycles is considered a standard of care for high-volume mCSPC based on the CHAARTED, STAMPEDE arm C, and GETUG-AFU 15 clinical trials.
- ADT plus abiraterone acetate continued until disease progression is considered a standard of care for all patients with mCSPC based on the LATITUDE and STAMPEDE arm G clinical trials.
- Predictive biomarkers are needed to select patients for ADT plus docetaxel versus ADT plus abiraterone. Until those are identified, ADT plus docetaxel may be considered for patients with mCSPC who have more than four metastases, have a good performance status, desire shorter total treatment time, or have concerns for prescription drug costs; ADT plus abiraterone acetate may be suggested to patients who have fewer than four sites of metastases or are unable/unwilling to tolerate the potential toxicity of chemotherapy.
- Multiple phase III clinical trials are investigating novel combinations of ADT and androgen axis inhibitors, including enzalutamide, apalutamide, darolutamide, and orteronel without corticosteroids in mCSPC.
- Clinical studies suggest that addition of surgery and/or radiotherapy to systemic treatment may have a role in the treatment of newly diagnosed mCSPC, and clinical trials are investigating this hypothesis.

Androgen-Deprivation Therapy Plus Docetaxel

To date, three clinical trials have investigated the efficacy of ADT plus docetaxel: CHAARTED, STAMPEDE arm C, and GETUG-AFU 15. CHAARTED was a phase III clinical trial that randomly assigned 790 men with mCSPC to receive ADT plus docetaxel or ADT alone. Docetaxel without daily prednisone was administered every 3 weeks for a total of six cycles. The primary outcome, median OS, was 13.6 months longer for patients treated with ADT plus docetaxel than for patients receiving ADT alone (57.6 months vs. 44.0 months, respectively; HR 0.61; 95% CI, 0.47–0.80). Of note, a substantial number of patients in the ADT-alone arm never received docetaxel at CRPC before death. ADT plus docetaxel also improved median time to progression compared with ADT alone (20.2 months vs. 11.7 months; HR 0.61; 95% CI, 0.51–0.72). Docetaxel has a significant toxicity profile that differs from that of ADT, and 29.3% of patients treated with ADT plus docetaxel reported any grade 3/4 adverse events. The most frequently reported grade 3/4 adverse
events were neutropenia (12.1%) and fatigue (4.1%). To determine whether ADT plus docetaxel should be used in all patients with mHSPC or only higher-risk patients, CHAARTED performed a subgroup analysis of median OS by extent of disease present. Investigators found that only patients with high-volume disease, defined as the presence of visceral metastases or at least four bone lesions with one or more beyond the vertebral bodies and pelvis, benefit from ADT plus docetaxel (median OS, 51 months vs. 34 months; HR 0.63; 95% CI, 0.50–0.79), whereas low-volume patients have similar outcomes with ADT alone or with docetaxel (median OS, 64 months vs. not reached; HR 1.04; 95% CI, 0.70–1.55).

GETUG-AFU 15, conducted before CHAARTED, was a phase III clinical trial that randomly assigned 385 men with mCSPC to receive ADT alone or ADT plus docetaxel. Median OS was not significantly improved in the ADT plus docetaxel arm compared with ADT alone (58.9 months vs. 54.2 months; HR 1.01; 95% CI, 0.75–1.36). Furthermore, before use of granulocyte colony-stimulating factor, four treatment-related deaths occurred in the ADT plus docetaxel arm. After publication of CHAARTED, a follow-up analysis of GETUG-AFU 15 reported median OS by volume of disease, which was collected retrospectively. A nonsignificant trend toward improved OS was seen in high-volume disease (39.8 months vs. 35.1 months; HR 0.78; 95% CI, 0.56–1.09), and no difference in OS was observed for low-volume disease (not reached vs. 83.4 months; HR 1.02; 95% CI, 0.67–1.55).

With discordant findings between CHAARTED and GETUG-AFU 15, STAMPEDE arm C sought to further explore whether ADT plus docetaxel improves survival for patients with mCSPC. STAMPEDE randomly assigned 2,962 men with locally advanced or mCSPC to receive ADT alone (arm A); ADT plus zoledronic acid (arm B); ADT plus docetaxel (arm C); or ADT, docetaxel, and zoledronic acid (arm E). Similar to CHAARTED, ADT plus docetaxel significantly improved median OS compared with ADT alone in STAMPEDE arm C (81 months vs. 71.3 months; HR 0.78; 95% CI, 0.66–0.93). ADT plus docetaxel also improved median failure-free survival compared with ADT alone (37 months vs. 20 months; HR 0.61; 95% CI, 0.53–0.70). As was seen in the other trials, more patients in the ADT plus docetaxel arm reported grade 3/4 adverse events than did those receiving ADT alone (39% vs. 17%), and one treatment-related death occurred in the ADT plus docetaxel cohort. Unfortunately, STAMPEDE did not report outcomes by volume of disease.

In a meta-analysis that included CHAARTED, STAMPEDE arm C/E, and GETUG-AFU 15, ADT plus docetaxel was confirmed to significantly improve median OS (HR 0.77; 95% CI, 0.68–0.87) and median failure-free survival (HR 0.64; 95% CI, 0.58–0.70) compared with ADT alone. These trials and subsequent meta-analysis established ADT plus docetaxel as a standard of care for fit patients with high-volume mCSPC.

**FIGURE 1. Androgen Synthesis Pathway Throughout Body With Drugs Targeting Androgen Synthesis**

Abbreviations: AR, androgen receptor; GnRH, gonadotropin-releasing hormone; HSP, heat shock protein; SARD, selective androgen receptor degrader.
ADT Plus Abiraterone Acetate Plus Prednisone
Similar to docetaxel, abiraterone acetate was initially approved for the treatment of mCRPC. Abiraterone is a nonsteroidal, irreversible inhibitor of CYP17A1, so it inhibits gonadal and extragonadal androgen synthesis. To date, two clinical trials studying abiraterone in mCSPC have been reported, LATITUDE and STAMPEDE arm G; one study, PEACE-1, is still ongoing. LATITUDE was a phase III clinical trial that randomly assigned 1,199 men with mCSPC to receive ADT plus abiraterone (1,000 mg daily) and prednisone (5 mg daily) or ADT alone. To be included in the trial, men with mCSPC needed to have at least two high-risk prognostic factors, including a Gleason score of 8 or higher, presence of at least three bone lesions, or measurable visceral metastases. LATITUDE was powered to measure two primary endpoints: median OS and radiographic progression-free survival. ADT plus abiraterone significantly improved median OS (not reached vs. 34.7 months; HR 0.62; 95% CI, 0.51–0.76) and median radiographic progression-free survival (33.0 vs. 14.8 months; HR 0.47; 95% CI, 0.39–0.55). Regarding toxicity, grade 3/4 adverse events were more common in the ADT plus abiraterone arm (63% vs. 48%). The most frequently reported grade 3/4 adverse events in the abiraterone arm were mineralocorticoid-related hypertension (20%), hypokalemia (11%), and increased alanine aminotransferase levels (5%).

Interestingly, in 2017, STAMPEDE arm G, which was simultaneously presented with LATITUDE at the ASCO annual meeting, showed similar benefits with upfront abiraterone. STAMPEDE arm G was a phase III clinical trial that included multiple cohorts of patients with advanced prostate cancer, including mCSPC, node-positive disease, or high-risk locally advanced disease. In total, 1,917 men with advanced prostate cancer were randomly assigned to receive ADT plus 1,000 mg of abiraterone plus 5 mg of prednisolone or ADT alone. Of these 1,917 men, 941 had newly diagnosed mCSPC. In the overall cohort, ADT plus abiraterone demonstrated a strong OS advantage compared with ADT (83% vs. 76%; HR 0.63; 95% CI, 0.52–0.76) and better 3-year failure-free survival (75% vs. 45%; HR 0.29; 95% CI, 0.25–0.34). In patients with mCSPC, the effect of ADT plus abiraterone on OS and failure-free survival remained true. As was seen in LATITUDE, the incidence of grade 3/4 adverse events was higher in the ADT plus abiraterone group than in the ADT-alone group (47% vs. 33%). On the basis of the results from the LATITUDE and STAMPEDE arm G clinical trials, ADT plus abiraterone acetate and prednisone is now considered a standard of care for mCSPC regardless of the disease volume status. However, follow-up for nonmetastatic prostate cancer is not adequate to determine the benefit.

A third phase III clinical trial evaluating ADT plus abiraterone is in progress. PEACE-1 will randomly assign 916 patients with mCSPC to one of four arms: ADT with or without docetaxel, ADT with or without docetaxel and abiraterone and prednisone, ADT with or without docetaxel and radiotherapy, or ADT with or without docetaxel and abiraterone and prednisone. PEACE-1 will help us better understand whether docetaxel and abiraterone can have synergistic effect in mCSPC.

OPTIMAL CURRENT TREATMENT PARADIGM
Because clinical trials investigating ADT plus docetaxel and ADT plus abiraterone had very similar outcomes and head-to-head, prospective comparisons were not performed, clinicians face a new challenge optimizing treatment selection for patients with mCSPC. Furthermore, predictive biomarkers are not available in the clinic to help guide treatment selection. Although the efficacy of these regimens is similar, the toxicity profiles, cost, and duration of treatment can help guide selection between docetaxel and abiraterone.

Analysis of the individual trials shows that the disease volume may help tailor treatment selection. In CHAARTED and GETUG-AFU 15, men with low-volume disease did not benefit with docetaxel. However, none of the trials with abiraterone have categorized men according to the volume status of the disease and thus have not shown lack of benefit in any given subset of patients. We recommend that docetaxel be considered for patients with high-volume disease, and abiraterone can be recommended to all regardless of disease volume (Table 1). Table 1 shows considerations for the treating physician choosing between ADT plus abiraterone and ADT plus docetaxel.

In regard to toxicity, the frequency of grade 3 to 5 adverse events was similar between ADT plus docetaxel and ADT plus abiraterone plus prednisone. However, the profile of adverse events significantly differs between the two drugs. Docetaxel may cause bone marrow suppression, infections, and neuropathy, whereas abiraterone may cause mineralocorticoid-induced hypertension, hypokalemia, and elevated liver enzyme levels. In general, most patients better tolerate abiraterone than docetaxel. The duration of treatment also differs significantly between the reported regimens of docetaxel and abiraterone in mCSPC. Docetaxel is given once every 3 weeks for a total of six cycles, which is generally around 15 weeks of total treatment. In contrast, abiraterone is recommended daily until time of progression, which generally occurs after several years of treatment with abiraterone. Finally, the expense to the patient of abiraterone and docetaxel differs significantly. When only cost per cycle and number of cycles given are considered, the six cycles of docetaxel cost the same as 3- to 4-month treatment

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Favors Abiraterone</th>
<th>Favors Docetaxel</th>
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<tr>
<td>Efficacy in HVD</td>
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<td>X</td>
</tr>
<tr>
<td>Efficacy in LVD</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
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<td></td>
<td>X</td>
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<tr>
<td>Cost</td>
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</tbody>
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Abbreviations: ADT, androgen-deprivation therapy; HVD, high-volume disease; LVD, low-volume disease.

TABLE 1. Attributes of Treatment That Favor ADT Plus Abiraterone or ADT Plus Docetaxel
with abiraterone. Additionally, there is frequently a high copay with abiraterone (an oral drug) compared with docetaxel (an intravenous drug).28,29 This is a simplistic analysis that does not account for many components of cost-effectiveness; however, a formal cost-effectiveness analysis has yet to be done. Thus, docetaxel may be favored over abiraterone for patients or in countries where cost factors heavily influence the treatment decision.

In summary, ADT plus docetaxel may be considered for patients who desire shorter total treatment time or when there are cost considerations. ADT plus abiraterone can be considered in patients who have low-volume disease, desire to avoid possible chemotherapy toxicity, or want to minimize facility visits for docetaxel administration. Finally, patient-specific comorbidities may guide treatment selection, for example, avoiding docetaxel in frail patients at high risk for myelosuppression and those with neuropathy and avoiding abiraterone plus prednisone in those with liver disease, diabetes, and osteoporosis.

NOVEL COMBINATIONS BEING INVESTIGATED FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

With the knowledge that deeper androgen signaling blockade leads to improved outcomes in mCSPC and the recent success of docetaxel and abiraterone, several novel combinations of ADT plus androgen axis inhibitors are under investigation. Enzalutamide is a second-generation antiandrogen that binds to the AR with higher affinity than bicalutamide and prevents nuclear translocation of the AR (Fig. 1).30 Enzalutamide is approved as any-line treatment of mCRPC.31,32 Two phase III clinical trials are evaluating ADT plus enzalutamide in patients with mCSPC: ENZA-MET and ARCHES (Table 2). ENZA-MET (NCT02446405) will randomly assign 1,000 patients with mCSPC to receive ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus placebo. Unfortunately, neither of these trials is comparing ADT plus enzalutamide to ADT plus abiraterone or docetaxel, which are now considered standard of care.

Apalutamide (ARN-509) is another second-generation antiandrogen that is an irreversible AR antagonist. Recently, in the SPARTAN trial in men with M0 CRPC, apalutamide showed improved survival outcomes; however, it is not currently approved for prostate cancer.33 ADT plus apalutamide is being studied for mCSPC in the phase III TITAN clinical trial (NCT02489318). Previously, a phase II clinical trial of apalutamide in mCRPC demonstrated acceptable safety and efficacy to warrant further investigations in mCSPC and mCRPC.34 TITAN is randomly assigning 1,000 patients with mCSPC to receive ADT with or without docetaxel plus apalutamide versus ADT alone (Table 2). TITAN will answer the question of whether addition of apalutamide to standard-of-care treatment may improve survival outcomes in mCSPC.

Darolutamide (ODM-201) is a next-generation antiandrogen that has a higher affinity for the AR than does enzalutamide or apalutamide.35 Darolutamide is not currently approved for the treatment of prostate cancer. However, a phase I/II clinical trial in 134 men with progressive mCRPC found darolutamide to have an acceptable safety profile.36 ARASENS (NCT02799602) is a phase III clinical trial in mCSPC that will randomly assign 1,300 men to receive ADT plus docetaxel and either darolutamide or placebo (Table 2). ARASENS is expected to read out in 2022.

Orteronel (TAK-700) is unique from the other novel androgen axis inhibitors discussed because it is a reversible CYP17 inhibitor that has more specificity for 17,20 lyase than 17 hydroxylase. Preclinical studies demonstrated that orteronel significantly reduces testosterone and androstenedione levels in cell lines and rats, resulting in smaller prostates.37,38 Although phase III clinical trials in mCRPC showed no OS benefit with orteronel, a phase II trial in patients with nonmetastatic prostate cancer and biochemical recurrence

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**TABLE 2. Ongoing and Recently Reported Phase III Clinical Trials Evaluating Novel Androgen Axis Inhibitors in Metastatic Hormone-Sensitive Prostate Cancer**

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Arms</th>
<th>No. of Patients</th>
<th>Primary Endpoint</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Anticipated Read Out</th>
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</thead>
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<tr>
<td>PEACE-1</td>
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<td>rPFS, OS</td>
<td>NCT01957436</td>
<td>2020</td>
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<td>SWOG-1216</td>
<td>ADT + TAK-700 vs. bicalutamide</td>
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<td>OS</td>
<td>NCT018909691</td>
<td>2020</td>
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<tr>
<td>ARASENS</td>
<td>ADT + doce + ODM-201 vs. placebo</td>
<td>1,300</td>
<td>OS</td>
<td>NCT02799602</td>
<td>2022</td>
</tr>
<tr>
<td>ENZA-MET</td>
<td>ADT ± doce + enza vs. NSAA</td>
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<td>OS</td>
<td>NCT02446405</td>
<td>2020</td>
</tr>
<tr>
<td>ARCHES</td>
<td>ADT ± doce + enza vs. placebo</td>
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<td>rPFS</td>
<td>NCT02677896</td>
<td>2023</td>
</tr>
<tr>
<td>STAMPEDE ARM J</td>
<td>ADT ± doce, ± RT, ± abi + enza</td>
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<td>OS</td>
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<td>2020</td>
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<td>TITAN</td>
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<td>1,000</td>
<td>rPFS, OS</td>
<td>NCT02489318</td>
<td>2021</td>
</tr>
</tbody>
</table>

Abbreviations: ADT, androgen-deprivation therapy; doce, docetaxel; RT, radiotherapy; abi, abiraterone acetate; rPFS, radiographic progression-free survival; OS, overall survival; enza, enzalutamide; NSAA, nonsteroidal androgen antagonist; apa, apalutamide.

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A synergistic effect with docetaxel. ARCHES (NCT02677896) aims to answer the same clinical questions. ARCHES is also randomly assigning 1,100 patients to receive ADT with or without docetaxel plus enzalutamide or ADT with or without docetaxel plus placebo. Unfortunately, neither of these trials is comparing ADT plus enzalutamide to ADT plus abiraterone or docetaxel, which are now considered standard of care.

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found that orteronel decreased PSA by greater than 30% in most patients and that 16% achieved a PSA less than 0.2 ng/mL at 3 months. A phase III clinical trial, SWOG-1216, is investigating ADT plus orteronel (without prednisone) compared with ADT plus bicalutamide in 1,304 patients with mCSPC (NCT01809691).

THE ROLE OF LOCALIZED THERAPY IN METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Prostate radiation or radical prostatectomy (RP) are not currently recommended for the treatment of patients with de novo metastatic prostate cancer. In some advanced malignancies, such as metastatic renal cell carcinoma, patients experience a survival benefit from cytoreductive surgery, which is considered a standard of care for these patients. This has led to increased interest in the role of local therapy for mCSPC. Although reported studies have important limitations, early results for this approach in mCSPC are intriguing and warrant further investigation.

Initially, two hypothesis-generating, retrospective Surveillance, Epidemiology, and End Results (SEER) database studies found that local therapy combined with systemic therapy improved survival in metastatic prostate cancer. In the first SEER analysis, 8,185 patients with stage IV prostate cancer were identified between 2004 and 2010. Of these 8,185 patients, 245 patients (3.0%) had an RP performed, and 129 patients (1.6%) were treated with prostate brachytherapy. The remaining, untreated patients were significantly older (p < .001) and less likely to have a Gleason score of 7 or lower (p < .001). Five-year OS and cancer-specific survival were higher in patients receiving RP (67.4% and 75.8%, respectively) and brachytherapy (52.6% and 61.3%) than in those receiving no local treatment (22.5% and 48.7%; p < .001).

Another SEER study used a propensity score analysis to ensure that the observed effect of radical prostatectomy or brachytherapy were attributable to treatment instead of baseline cohort differences. The authors confirmed that RP and brachytherapy improve CSS compared with no definitive treatment. Because of their use of the SEER database, both studies had substantial limitations, including not accounting for whether patients received ADT and the fact that less than 5% of their total cohorts received definitive therapy. A third retrospective study used the National Cancer Database to confirm the findings from previous SEER studies. Of 6,382 men with newly diagnosed mCSPC in this database, 538 men (8.4%) were treated with ADT plus radiotherapy, and the remaining men were treated with ADT alone. Men treated with ADT plus radiotherapy had significantly improved OS in multivariate analysis (HR 0.62; 95% CI, 0.55–0.71).

To address the limitations of the prior SEER studies, a study linked SEER outcomes to Medicare data. This study design allowed the authors to account for medical comorbidities, receipt of ADT, and type of radiotherapy given (palliative, localized intensity-modulated radiation, or conformal radiation). In the multivariate analysis accounting for these factors, prostate cancer–specific mortality was improved for RP (HR 0.48; 95% CI, 0.27–0.85) and intensity-modulated radiation (HR 0.38; 95% CI, 0.24–0.61). Because the three prior studies came from the U.S. SEER database, a retrospective study of the Munich Cancer registry also looked at the effect of RP on survival for mCSPC. Of the 1,538 men with mCSPC, 75 men (5%) received RP, and this group had improved 5-year OS compared with the no-surgery arm (55% vs. 21%; p < .01). Finally, a case-control series of 140 men with mCSPC randomly assigned 38 men to prostate radiotherapy, 39 to palliative radiotherapy, and 63 to no radiotherapy. Patients who received prostate radiotherapy had improved 3-year OS compared with the other groups (69% vs. 43%; p = .004), and no grade 3 or worse genitourinary adverse events were reported.

In summary, RP and local radiotherapy have shown potential to improve survival in patients with mCSPC. However, the design of reported studies (i.e., retrospective or case-control series) and inconsistent findings indicate that randomized clinical trials are needed before definitive therapy is routinely used in the management of newly diagnosed mCSPC. A phase II clinical trial randomly assigning 180 men with mCSPC to ADT with or without localized therapy (NCT01751438) is underway and should begin to address this hypothesis. As clinical trials investigate these questions, investigators must consider how the significant morbidity associated with definitive therapy weighs against the benefits of treatment.

METASTASIS-DIRECTED THERAPY FOR OLIGOMETASTATIC PROSTATE CANCER

Although no consensus definition exists, oligometastatic prostate cancer is often defined as at least three or five metastases. To date, it is unclear whether patients with oligometastatic prostate cancer should be treated differently than patients with high-volume disease.

Multiple retrospective studies initially suggested that metastasis-directed therapy is safe, feasible, and efficacious in patients with oligometastatic prostate cancer. In a single-center study of 40 patients with fewer than two bone metastases in the spine, stereotactic body radiation therapy (SBRT) to the metastatic lesions was associated with an estimated local disease control rate of 95.5% at 6, 12, and 24 months. Another single-center study of 21 patients with oligometastatic disease involving the bone (19 patients), lymph nodes (one patient), or liver (one patient) found that SBRT had 100% local control at 5 months and that 53% of patients had an undetectable PSA. These studies were followed by a multicenter retrospective study of 119 patients that confirmed SBRT is efficacious in oligometastatic prostate cancer. Then, two retrospective studies demonstrated that SBRT delays the initiation of ADT for patients with oligometastatic disease.

With multiple retrospective studies suggesting that metastasis-directed therapy may be efficacious for oligometastatic prostate cancer, a phase II clinical trial, STOMP, sought to validate the role for metastasis-directed therapy. In STOMP, 62 patients with biochemical recurrence after
definitive therapy or fewer than three extracranial metastatic lesions were randomly assigned to surveillance or metastasis-directed therapy (either SBRT or surgery). The median ADT-free survival for surveillance was 13 months compared with 21 months for the metastasis-directed therapy arm (HR 0.60; 95% CI, 0.40–0.90). Quality of life was similar in the two arms at baseline, 3 months, and 12 months. Two ongoing phase III clinical trials, CORE and PCX IX, will provide overall survival data for metastasis-directed therapy. CORE (NCT02759783) is randomly assigning 206 patients with oligometastatic prostate, breast, and non–small cell lung cancer to standard of care or standard of care plus SBRT. In contrast, PCX IX (NCT02685397) is randomly assigning 130 patients with oligometastatic CRPC to an LHRH agonist plus enzalutamide or to LHRH agonist plus enzalutamide plus SBRT.

CONCLUSION
ADT plus docetaxel and ADT plus abiraterone are the contemporary standard treatment of mCSPC. ADT plus docetaxel may be considered for patients with mCSPC who have good performance status, have high-volume disease, desire shorter total treatment time, or have concerns of prescription drug costs. ADT plus abiraterone acetate may be suggested for men with cancer of any volume and who desire to minimize hospital visits associated with chemotherapy infusions. Patient-specific comorbidities may guide treatment selection as well; for example, abiraterone plus prednisone may be avoided in those with diabetes, liver disease, osteoporosis, or difficult-to-control hypertension, and docetaxel may be avoided in those with neuropathy or at high risk for myelosuppression. Eventually, we need predictive biomarkers to optimize treatment selection between these current and emerging therapies. We also anticipate that treatment of mCSPC will continue to rapidly evolve. Multiple novel androgen axis inhibitors are being investigated in combination with ADT for treatment of mCSPC. On the basis of retrospective and case-control series data, local therapy for de novo mCSPC has the potential to augment current systemic therapies. Finally, for patients with oligometastatic prostate cancer, metastasis-directed therapy combined with systemic therapy is promising.

References


Practical Methods for Integrating Genetic Testing Into Clinical Practice for Advanced Prostate Cancer

Heather Cheng, MD, PhD, Jacquelyn Powers, LCGC, Kerry Schaffer, MD, and Oliver Sartor, MD

OVERVIEW

Recent advances clearly demonstrate the potential clinical relevance of germline genetic testing and somatic genomic profiling in identifying possible therapeutic and/or clinical trial options, particularly in advanced prostate cancer. In addition, if a germline genetic mutation/pathogenic variant is identified, there may be important family implications and possible life-saving changes to healthcare management. However, there is substantial debate and uncertainty about how best to offer genetic testing services, which tests to use, which patients to test, what sequence of testing, what timing, by whom, and with what kind of follow-up. To help address this new area of potential benefit and confusion, we provide a practical overview of recent advances, discuss options and considerations for both germline and somatic testing, and offer practical advice on what providers should understand before referring and/or ordering testing, key discussion points for patients and families, and available genetics resources.

Over the past several years, it has become abundantly clear that molecular events not only can be defined in prostate cancer but also can affect the treatment of patients and can have important implications for family members.

A substantial proportion of aggressive prostate cancers (approximately 25%) have characteristic DNA repair alterations that suggest precision therapy opportunities; approximately 10% have alterations found in the germline and potentially represent inherited cancer predisposition. These findings have led to rapid and far-reaching changes to the field that include exciting new precision treatment opportunities and increased responsibility and challenges surrounding tumor genomic profiling and genetic counseling around inherited cancer risk.

GENOMICS VERSUS GENETICS AND IMPLICATIONS FOR PROSTATE CANCER CARE

In 2015, The Cancer Genome Atlas Research Network reported findings from 333 primary prostate cancers and the identification of 19% of primary tumors with mutations in DNA repair genes, including 3% in the homologous recombination repair gene, BRCA2.1 That same year, the International Stand Up to Cancer/Prostate Cancer Foundation/American Association for Cancer Research Prostate Cancer Dream Team applied exome sequencing to 150 metastatic biopsies and found that 23% of metastatic prostate cancers carry alterations in genes critical for DNA repair, again involving homologous recombination repair (BRCA2, ATM, and BRCA1) as well as mismatch repair (MLH1 and MSH2).2

Unexpectedly, 8% of the DNA repair mutations were found in the germline DNA, the first indication that there may be a higher than previously recognized prevalence of cancer predisposition among men with metastatic prostate cancer. These discoveries represented major strides in the field and a new era marked by greater interplay between somatic genomics and germline genetics.

HOMOLOGOUS RECOMBINATION DNA REPAIR DEFECTS AND NEW TREATMENT STRATEGIES

Specific treatment strategies could quickly be gleaned from research in other BRCA1/2-associated cancers, particularly breast cancer and ovarian cancer. The phase II TOPARP-A study showed that 14 of 16 patients (88%) with heavily pretreated metastatic castration-resistant prostate cancer and somatic alterations in DNA repair genes achieved objective responses to the PARP inhibitor olaparib.3 The identified genes involved included BRCA2, ATM, and BRCA1, among others (Table 1). The responses were sustained for a large portion of patients (in many, for more than 6 months). This trial highlights the strong potential therapeutic role for PARP inhibitor therapy in tumors with DNA repair defects and has led to a number of subsequent clinical trials testing PARP inhibitors for biomarker-selected (i.e., DNA repair-deficient) advanced prostate cancer.

Although PARP inhibitors are currently garnering the most attention in the clinical trial realm, platinum chemotherapy...
and has the advantage of being readily available and familiar to practicing medical oncologists. A retrospective case series evaluated three patients who displayed exceptional response (complete or partial response ranging from 6 to 30 months) to platinum chemotherapy after disease progression while receiving prior standard therapy and whose tumors were available for analysis. Clinical targeted next-generation sequencing on tumor DNA demonstrated the presence of biallelic BRCA2 inactivation: two patients had a single germline mutation with an additional acquired somatic event, and the third patient had two somatic mutations.

In a retrospective analysis of 141 men with prostate cancer who received at least two doses of carboplatin and docetaxel for metastatic castration-resistant prostate cancer, treatment demonstrated benefit for patients with germline DNA repair deficiency with BRCA2 mutation. Eight of 141 men (5.7%) had a pathologic germline mutation; six of these patients (75%) experienced a prostate-specific antigen decline greater than 50% within 12 weeks compared with 23 of 133 noncarriers (17%; absolute difference, 58%; 95% CI, 27% to 88%; p < .001). This retrospective analysis of a prospective study demonstrated increased response to platinum-based chemotherapy among patients with metastatic castration-resistant prostate cancer who also carried a BRCA2 germline mutation or pathogenic variant. A prostate-specific antigen response greater than 50% was associated with prolonged survival in the entire group of 141 men, and median survival was 18.9 months for carriers compared with 9.5 months for noncarriers.

These two studies highlight a biologic subgroup of prostate cancer with particular sensitivity to platinum therapy. In contrast, other studies of platinum have failed to show clinical benefit among unselected patients with prostate cancer, illustrating the concept that genomics and genetics together can help identify effective “precision” treatments for the subset of patients who are likely to respond and can minimize ineffective treatments for those who are unlikely to benefit. As a result of these data, other studies are ongoing to evaluate the role of PARP inhibitors and platinum-based chemotherapy alone or in combination with other therapy for patients with DNA repair defects.

GERMLINE DNA REPAIR DEFECTS ARE ASSOCIATED WITH POOR PROGNOSIS AND ENRICHED IN METASTATIC PROSTATE CANCER

Recognition of genomic factors critical to driving a cancer may aid in efforts toward characterizing natural history and thus may serve as prognostic markers. It has been established that men who carry relatively rare pathogenic germline variants in BRCA2 have an increased risk of developing prostate cancer and, if cancer is present, have worse outcomes compared with men with prostate cancer who do not carry BRCA2 pathogenic variants (mutations).

**TABLE 1. DNA Repair Genes, Prevalence of Mutations/Deletions in Metastatic Prostate Cancer, and Early Evidence of Therapeutic Response to PARP Inhibitors**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Prevalence of Germline Mutations in Metastatic Prostate Cancer (%)</th>
<th>Preliminary Association With PARP Inhibitor Response (X)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>1.59</td>
<td>X</td>
</tr>
<tr>
<td>ATR</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>BAP1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>BARD1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>BRCA1</td>
<td>0.87</td>
<td>X</td>
</tr>
<tr>
<td>BRCA2</td>
<td>5.35</td>
<td>X</td>
</tr>
<tr>
<td>BRIP1</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>CHEK2</td>
<td>1.87</td>
<td>X</td>
</tr>
<tr>
<td>FAM175A</td>
<td>0.18</td>
<td></td>
</tr>
<tr>
<td>FANCA</td>
<td>—</td>
<td>X</td>
</tr>
<tr>
<td>GEN1</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>HDAC2</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>MLH1</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>MRE11A</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>MSH2</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>MSH6</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>NBN</td>
<td>0.29</td>
<td>X</td>
</tr>
<tr>
<td>PALB2</td>
<td>0.43</td>
<td>X</td>
</tr>
<tr>
<td>PMS2</td>
<td>0.29</td>
<td></td>
</tr>
<tr>
<td>RAD51C</td>
<td>0.14</td>
<td></td>
</tr>
<tr>
<td>RAD51D</td>
<td>0.43</td>
<td></td>
</tr>
<tr>
<td>XRCC2</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

*Data are from Pritchard et al.

**TABLE 1. DNA Repair Genes, Prevalence of Mutations/Deletions in Metastatic Prostate Cancer, and Early Evidence of Therapeutic Response to PARP Inhibitors**

**PRACTICAL APPLICATIONS**

- The presence of both germline and somatic mutations is increasingly well defined for patients with advanced prostate cancer; however, who to test and how to test is the subject of considerable debate.
- It is now clear that the prevalence of men with metastatic prostate cancer carrying pathologic variants in DNA repair mutations is approximately 10% and includes genes such as BRCA2 (most predominant), ATM, CHEK2, BRCA1, RAD51D, and PALB2.
- Surprisingly, family histories for these patients are not always revealing and thus cannot be relied on to guide genetic testing.
- Germline pathogenic alterations may have both familial and therapeutic implications.
- Somatic alterations in various genes are increasingly well described; PARP inhibitors or platinum-based therapies may be considered for patients with BRCA mutations, and treatment with PD-1 inhibitors is warranted for patients with mismatch repair alterations and has been approved by the U.S. Food and Drug Administration.
A retrospective study of tumor characteristics in BRCA1/2 germline pathogenic variant (PV; mutation) carriers versus noncarriers identified that 67 participants in the carrier group had more aggressive tumors, a significantly higher T score (T1, 9% vs. 26%; T2, 48% vs. 39%; and T3, 34% vs. 28%; p < .02), and a higher Gleason score (≤ 6, 33% vs. 49%; 7, 31% vs. 34%; and ≥ 8, 34% vs. 15%; p < .0001) compared with 1,235 noncarriers. N1 disease was present in 6% of carriers and 2% of noncarriers (p = .009). Moreover, BRCA1/2 germline carriers treated with curative intent with conventional treatment strategies (49 with BRCA2 and 18 with BRCA1) developed metastatic disease earlier and were observed to have shorter survival compared with 1,235 noncarriers. Independent of the more aggressive baseline tumor characteristics, BRCA1/2 mutation carriers had worse outcomes in terms of metastasis-free survival (90%, 72%, and 50% vs. 97%, 94%, and 84% at 3, 5, and 10 years, respectively) and cause-specific survival (96%, 76%, and 61% vs. 99%, 97%, and 85% at 3, 5, and 10 years, respectively) compared with individuals who were noncarriers.

The prevalence of germline DNA repair alterations associated with high- and moderate-penetrance cancer predisposition is higher than previously recognized in the population with metastatic prostate cancer. An analysis of germline mutations among men with metastatic prostate cancer was performed to determine the frequency of germline DNA repair mutations in this population. This analysis tested 20 genes associated with autosomal dominant cancer predisposition among 692 men with metastatic prostate cancer and identified 84 pathogenic germline mutations (11.8%) in 16 different genes (Table 1). The study used whole-exome sequencing or targeted next-generation sequencing assays specific for the DNA repair genes. The 11.8% frequency of germline mutations in genes mediating DNA repair processes in men with metastatic prostate cancer showed a significantly higher prevalence than that for patients with localized prostate cancer (4.6%; per the Cancer Genome Atlas Research Network) and for patients without cancer (2%–3%; per the Exome Aggregation Consortium). Tumor was available for sequencing for 61% of patients without cancer (2%–3%; per the Exome Aggregation Consortium) and 4.6%; per the Cancer Genome Atlas Research Network). The study used whole-exome sequencing or targeted next-generation sequencing assays specific for the DNA repair genes. The 11.8% frequency of germline mutations in genes mediating DNA repair processes in men with metastatic prostate cancer showed a significantly higher prevalence than that for patients with localized prostate cancer (4.6%; per the Cancer Genome Atlas Research Network) and for patients without cancer (2%–3%; per the Exome Aggregation Consortium).

Tumor was available for sequencing for 61% of patients without cancer (2%–3%; per the Exome Aggregation Consortium) and 4.6%; per the Cancer Genome Atlas Research Network). The study used whole-exome sequencing or targeted next-generation sequencing assays specific for the DNA repair genes. The 11.8% frequency of germline mutations in genes mediating DNA repair processes in men with metastatic prostate cancer showed a significantly higher prevalence than that for patients with localized prostate cancer (4.6%; per the Cancer Genome Atlas Research Network) and for patients without cancer (2%–3%; per the Exome Aggregation Consortium).

In addition to the potential therapeutic benefits and prognostic implications, identifying germline carriers of single, high- or moderate-penetrance cancer predisposition genes is an opportunity for cascade genetic testing. Early germline genetic testing of family members will allow better understanding of personal risk for developing cancers and will create opportunities for early cancer-specific screening and, in some cases, risk reduction therapies and reproductive planning options. It should be noted that risk/penetrance for prostate cancer is incompletely characterized for many of the newly implicated genes but there are established guidelines for screening/management of other cancers for some genes. With the recent exciting advances, the extent of germline and somatic testing is likely to increase. Ongoing efforts are underway to understand and optimize delivery models, timing, and other considerations around germline and somatic genetic testing. In the meantime, we offer the following practical considerations.

**PRECISION MEDICINE FOR PROSTATE CANCER IN THE REAL WORLD: SOMATIC AND GERMLINE TESTING CONSIDERATIONS**

Obtaining specimens from prostate cancer samples can be challenging for numerous reasons. First, metastatic biopsies are more invasive procedures and the most common site of metastatic disease is bone, which poses some difficulty with specimen acquisition, and can potentially involve specimen processing steps that may interfere with sequencing assays (e.g., decalcification). Second, there can be heterogeneity within the tumor tissue; thus, limitations of sampling may lead to results only partially reflective of tumor biology. Tumor sampling techniques and circulating tumor cell (CTC) sequencing methods are not yet agreed upon in the experimental realm or as standard of care. However, progress is being made through advances in technology and

<table>
<thead>
<tr>
<th>SIDEBAR 1. Suggested Criteria for Whom to Offer Genetic Counseling/Testing for Germline Alterations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Man With a Diagnosis of Prostate Cancer and Any One of the Following:</strong></td>
</tr>
<tr>
<td>• Known mutation in a cancer susceptibility gene within the family</td>
</tr>
<tr>
<td>• Metastatic prostate cancer</td>
</tr>
<tr>
<td>• High-risk localized prostate cancer (Gleason score ≥ 8, WHO grade group ≥ 3, or PSA ≥ 20)</td>
</tr>
<tr>
<td>• Tumor (somatic) sequencing indicating the presence of mutations in hereditary cancer risk genes (e.g., <strong>BRCA2, BRCA1, ATM, MSH2, MSH6, MLH1, PMS2</strong></td>
</tr>
<tr>
<td>• Family history suggestive of hereditary breast and ovarian cancer syndrome</td>
</tr>
<tr>
<td>• Family history suggestive of Lynch syndrome</td>
</tr>
<tr>
<td>• Family history suggestive of hereditary prostate cancer syndrome</td>
</tr>
</tbody>
</table>

increasing correlation between ctDNA and tumor tissue. An ideal test would provide information about somatic mutations (and germline mutations if desired), would have low cost, and would be easy to obtain. Ultimately, if a test were simple and affordable, somatic and germline assessment of a tumor at diagnosis could someday help physicians guide up-front management and potentially monitor for resistance and guide subsequent treatment planning.

AVAILABILITY OF GERMLINE TESTING

Currently, germline genetic testing may be slightly more straightforward, because germline variants and mutations can be easily and reliably evaluated from peripheral blood and saliva as well as from buccal mucosa or skin biopsy and there are accepted standards for reporting variants (benign, likely benign, variant of uncertain significance, pathogenic, and likely pathogenic).11

Several options for testing are present and the exact test is dependent on arrangements that can be made individually. Companies such as Ambry Genetics, Color Genomics, Invitae Genetics, and Myriad all have different mechanisms for testing and billing. A key determination is the “out-of-pocket” cost to the patient and what will be paid by insurance, which can be difficult to discern. Many patients are interested in genetic testing because of the familial implications but out-of-pocket costs are a consideration for many.

It is also notable that the patients with advanced prostate cancer may or may not have family histories that qualify them for genetic testing, and at times the criteria seem to vary from one insurance company to another. Testing guidelines for men are less established than those for women.

Another issue that has been extremely problematic is the frequent lack of availability of genetic counselors. This has become a controversial area particularly for clinics that treat patients who may be traveling from distant locations. It may be helpful to create a standardized set of materials and information for patients and a mechanism for testing to occur directly in an oncology clinic without formal genetic counseling if access to counseling is a limited resource. This is a potentially controversial approach, yet the limitations of genetic counseling resources are substantial in many institutions and this could facilitate triaging of more in-depth genetics services for individuals who have variants of significance. Some companies offer genetic counseling services over the telephone. Clearly, this is an area that requires further development and collaborative optimization.

WHO TO TEST FOR GERMLINE ALTERATIONS?

There are multiple questions that arise regarding who should be tested, how, and when. A consensus document was recently published but must be considered exploratory in terms of making recommendations simply because of the lack of data.12 In addition, relevant National Comprehensive Cancer Network guidelines have been updated. The current National Comprehensive Cancer Network prostate guidelines (www.nccn.org) recommend that genetic counseling and/or testing be offered to patients with metastatic prostate cancer and those who qualify for the testing based on family history guidelines (Sidebar 1).

Patient priorities should be considered, as should cost of testing. Utility of results may be not only for the patient’s own prostate cancer care decisions (in which case life expectancy and performance status should be factored), but also to test an informative member of the family where cascade testing is also a potential goal. Potentially at-risk relatives would have the option for more informative, less expensive single-site testing if a pathogenic result is found.

ASSAYS FOR SOMATIC GENETIC ALTERATIONS

Evaluation of somatic alterations in prostate cancer continues to evolve. A variety of DNA, RNA, or protein-based assays can be either tissue or blood based. Tissue-based assays are well discussed in the context of other tumors and further discussions here do not need to be elaborated on other than to say that mutations and copy number variations are only part of the story. Inversions (e.g., the Boland inversion), methylation patterns (e.g., those relevant for MLH1), and splice variants are additional noteworthy areas. Tissue-based assays have recently been covered by selected insurance companies, including Medicare.

RNA transcriptomic analyses and the generation of various signatures are both interesting and potentially clinically relevant. PAM50 categorization into luminal and basal subtypes is potentially noteworthy for those with localized disease. Tissue- and blood-based assays have been developed on both androgen receptor (AR) amplification and AR splice variants (especially ARV-7). ARV-7 can be assayed in CTCs or in whole blood. Although the importance of ARV-7 has been debated, the stability of RNA is potentially problematic. RNA-based ARV-7 assays in CTCs are cleared by the Clinical Laboratory Improvement Amendment and can be ordered from selected vendors.

A variety of protein-based assays have been studied, with ARV-7 being a recent protein of focus. The small aberrant extension of the ARV-7 protein (at the C terminus) can be targeted with specific antibodies. Antibody-based assays for ARV-7 can be done on CTCs. Such testing can soon be commercially available.

Another blood-based assay is based on cell-free DNA or ctDNA. There is clear progress on both mutations and amplifications of AR. Non-AR assays have yet to be verified but understanding the mutations in DNA repair genes, mismatch repair genes, and microsatellite instability/mutation burden is a current area of assessment. Such assays can now be ordered from various commercial vendors but their coverage by insurance is highly variable.

CLINICAL ACTIONABILITY OF SOMATIC MUTATIONS

At present, the most clinically “actionable” alteration may be the presence of mismatch repair mutations or high
mismatch repair is a bit of a conundrum. Who to test? Lynch currently exist. Based ctDNA assays for use of PARP inhibitors or platinum may be justified. To our knowledge, no data on blood-somatic mutations. The use of platinum in an empirical manner may be warranted for patients with either germline alterations or family histories that are suspect for Lynch-type patterns. The frequency of microsatellite instability and mismatch repair is unclear but estimates ranged as high as 12% of patients in an autopsy series.17

PRACTICAL GUIDANCE ON GENETIC COUNSELING WITHOUT GENETIC COUNSELOR SUPPORT

As next-generation tumor sequencing becomes more embedded into routine clinical oncology practice, it remains critically important that practitioners recognize and better understand its role in potentially unearthing germline or inherited cancer risk. Although the primary objective of next-generation tumor sequencing is to determine therapeutic targets, results may also suggest or identify underlying germline disease-associated variants regardless of whether they were suspected prior to testing.18 It could be argued that “germline genetics” is best approached via thorough risk assessment under the provision of a specialist such as a genetic counselor. Although this is considered the “gold standard,” the avenues by which individuals are assessed for inherited cancer risk, including “incident to” next-generation tumor sequencing, have altered the mechanisms of ascertainment. When specialist support is not available, the traditional approach of pre- and postgenetic counseling may be untenable.

This section will review practical guidance and tools to help demystify and make “germline versus somatic” more navigable.

The main components of clarifying and demystifying germline versus somatic variants are as follows: (1) know the test and what is or is not reported, (2) identify the laboratory contact(s) and/or laboratory genetic counselor, (3) have general familiarity with genes or findings that could be relevant to inherited susceptibility, and (4) understand how to triage. Through this foundation, one can have better-informed conversations with patients and their families.

Germline Versus Somatic

In distinguishing between germline and somatic variants, germline DNA is inherited material from both the egg and sperm that may be passed down to offspring. A germline PV is constitutional and within every cell of the body. With few exceptions, germline PVs that predispose to known inherited cancer syndromes (e.g., BRCA1/2 and hereditary breast and ovarian cancer syndrome) are inherited in an autosomal dominant manner. Put another way, each child (offspring) has a 50/50 chance of inheriting the germline PV and associated cancer risks. Approximately 5% to 10% of cancers are inherited and are attributable to a single highly penetrant PV in a DNA repair gene.
Somatic variants are alterations in genes that develop over one’s lifetime, and they are not present in the egg or sperm and cannot be passed down to offspring. In this context, should one pursue analysis of this mutation through a blood or saliva specimen, the PV would be absent. The majority of genetic alterations detected in tumors are somatic (“It’s not you, it’s your tumor.”).
### TABLE 4. Genes Associated With Increased Risk of Cancer

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome Association</th>
<th>Predominant Tumor Type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High penetrance</strong></td>
<td>Consistent phenotype: available clinical diagnostic criteria, early onset, multigenerational, specific constellation of clinical features in individual +/- family</td>
<td></td>
</tr>
<tr>
<td>APC</td>
<td>FAP</td>
<td>Colorectal, polyposis (adenomatous)</td>
</tr>
<tr>
<td>BAP1</td>
<td>Renal, uveal melanoma</td>
<td></td>
</tr>
<tr>
<td><strong>BRCA1</strong></td>
<td>HBOC</td>
<td>Breast, ovarian, prostate, pancreas, melanoma</td>
</tr>
<tr>
<td><strong>BRCA2</strong></td>
<td>HBOC</td>
<td>Breast, ovarian, prostate, pancreas, melanoma</td>
</tr>
<tr>
<td><strong>BMPR1A</strong></td>
<td></td>
<td>Colorectal, large and small bowel polyposis (juvenile type)</td>
</tr>
<tr>
<td><strong>CDH1</strong></td>
<td>Hereditary diffuse gastric cancer</td>
<td>Diffuse gastric, breast</td>
</tr>
<tr>
<td><strong>CDK4</strong></td>
<td>Melanoma cancer syndrome (FAMMM)</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td><strong>CDKN2A</strong></td>
<td>Melanoma cancer syndrome (FAMMM)</td>
<td>Malignant melanoma</td>
</tr>
<tr>
<td><strong>FH</strong></td>
<td>Hereditary leiomyomatosis and renal cell cancer</td>
<td>Renal, cutaneous, and uterine leiomyomas</td>
</tr>
<tr>
<td><strong>FLCN</strong></td>
<td>Birt Hogg-Dubé</td>
<td>Renal, fibrofolliculomas, pneumothorax, lung cysts</td>
</tr>
<tr>
<td><strong>MEN1</strong></td>
<td>Multiple endocrine neoplasia type 1</td>
<td>Endocrine[b]</td>
</tr>
<tr>
<td><strong>MLH1</strong></td>
<td>HNPCC, Lynch syndrome</td>
<td>Tier 1: colorectal, endometrial, ovarian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tier 2: gastric, small bowel, brain, pancreas, prostate</td>
</tr>
<tr>
<td><strong>MSH2</strong></td>
<td>HNPCC, Lynch syndrome</td>
<td>Tier 1: colorectal, endometrial, ovarian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tier 2: gastric, small bowel, brain, pancreas, prostate</td>
</tr>
<tr>
<td><strong>MSH6</strong></td>
<td>HNPCC, Lynch syndrome</td>
<td>Tier 1: colorectal, endometrial, ovarian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tier 2: gastric, small bowel, brain, pancreas, prostate</td>
</tr>
<tr>
<td><strong>RB1</strong></td>
<td></td>
<td>Tier 2: gastric, small bowel, brain, pancreas, prostate</td>
</tr>
<tr>
<td><strong>RET</strong></td>
<td>Retinoblastoma (pediatric), melanoma, sarcoma</td>
<td>Medullary thyroid</td>
</tr>
<tr>
<td><strong>PALB2</strong></td>
<td></td>
<td>Breast, pancreas</td>
</tr>
<tr>
<td><strong>PMS2</strong></td>
<td>HNPCC, Lynch syndrome</td>
<td>Tier 1: colorectal, endometrial, ovarian</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tier 2: gastric, small bowel, brain, pancreas, prostate</td>
</tr>
<tr>
<td><strong>PTEN</strong></td>
<td>Cowden syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>SDHA</strong></td>
<td>Hereditary pheochromocytoma-paraganglioma</td>
<td>Pheochromocytoma, paraganglioma</td>
</tr>
<tr>
<td><strong>SDHB</strong></td>
<td>Hereditary pheochromocytoma-paraganglioma</td>
<td>Pheochromocytoma, paraganglioma</td>
</tr>
<tr>
<td><strong>SDHC</strong></td>
<td>Hereditary pheochromocytoma-paraganglioma</td>
<td>Pheochromocytoma, paraganglioma</td>
</tr>
<tr>
<td><strong>SDHD</strong></td>
<td>Hereditary pheochromocytoma-paraganglioma</td>
<td>Pheochromocytoma, paraganglioma</td>
</tr>
<tr>
<td><strong>STK11</strong></td>
<td>Peutz-Jegher syndrome</td>
<td>Tier 1: polyposis (Peutz-Jegher type), distinct lip freckling[b]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tier 2: breast, colorectal, pancreas, lung, small bowel</td>
</tr>
<tr>
<td><strong>TP53</strong></td>
<td>Li-Fraumeni syndrome</td>
<td>Pediatric adrenocortical carcinoma, choroid plexus tumor, breast cancer (younger than 35 years), soft tissue sarcoma</td>
</tr>
<tr>
<td><strong>TSC1</strong></td>
<td>Tuberous sclerosis type 1</td>
<td></td>
</tr>
<tr>
<td><strong>TSC2</strong></td>
<td>Tuberous sclerosis type 2</td>
<td></td>
</tr>
<tr>
<td><strong>VHL</strong></td>
<td>Von Hippel Lindau</td>
<td></td>
</tr>
<tr>
<td><strong>WT1</strong></td>
<td>Wilms tumor, including WAGR</td>
<td></td>
</tr>
<tr>
<td><strong>NF2</strong></td>
<td>Neurofibromatosis type 2</td>
<td></td>
</tr>
</tbody>
</table>

Continued
Deciphering What Is Somatic and What Could Be Germline: Know Your Test and Know Your Laboratory

More frequently seen in research-based next-generation tumor sequencing, although there will likely be an uptick in the pursuit of commercial entities, laboratories may sequence a normal, matched control DNA sample in parallel with the tumor DNA. When using “paired tumor-normal,” germline variants may be evident. In such cases, however, it is not always apparent whether germline variants are reported, and if they are, by what standard of interpretation and rigor. This section focuses on laboratories that sequence only the tumor DNA, because this is the more likely encountered scenario in the clinical realm. Tumor-only sequencing without matched normal DNA introduces the possibility of a germline mutation but does not confirm or rule it out. It is at the practitioner’s discretion when to suspect a reported mutation as

TABLE 4. Genes Associated With Increased Risk of Cancer (Cont’d)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome Association</th>
<th>Predominant Tumor Type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Moderate penetrance (monozygote)</td>
<td>Breast, pancreas</td>
</tr>
<tr>
<td>BRIP1</td>
<td>No established syndrome, inconsistent phenotype</td>
<td>Ovarian</td>
</tr>
<tr>
<td>CHEK2</td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>MITF</td>
<td></td>
<td>Breast, prostate, colon</td>
</tr>
<tr>
<td>NBN</td>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td>RAD51C</td>
<td></td>
<td>Breast</td>
</tr>
<tr>
<td>RAD51D</td>
<td></td>
<td>Ovarian</td>
</tr>
<tr>
<td>APC I1307K</td>
<td>Low penetrance</td>
<td>Colorectal</td>
</tr>
<tr>
<td>MUTYH</td>
<td></td>
<td>Colorectal</td>
</tr>
<tr>
<td>CHEK2 I157T</td>
<td></td>
<td>Breast</td>
</tr>
</tbody>
</table>

*Per National Comprehensive Cancer Network guidelines (v1.2018), all patients with somatic BRCA1 and BRCA2 pathogenic findings regardless of tumor type and/or family history should be offered germline confirmation.

*Clinical diagnosis typically made based on noncancerous features. Please refer to www.omim.org for explanation and expansion.

*Per the Cancer Genome Atlas Research Network, approximately 5% of primary prostate cancers have a PTEN mutation, with 0.1% germline frequency. Please refer to OMIM.org or ACMG-NSGC practice guidelines for appropriate consideration of germline confirmation and/or referral.

*Most frequently mutated gene in human cancers. Please refer to Online Mendelian Inheritance in Man (OMIM) or ACMG-NSGC practice guidelines for appropriate consideration of germline confirmation and/or referral.

Abbreviations: FAP, familial adenomatous polyposis; HBOC, heritable breast and ovarian cancer; FAMMM, familial atypical multiple mole–melanoma; HNPCC, hereditary nonpolyposis colorectal cancer; WAGR, Wilms tumor/aniridia/genitourinary malformation/mental retardation; ACMG, American College of Medical Genetics and Genomics; NSGC, National Society of Genetic Counselors.

TABLE 5. Ashkenazi Jewish and European Founder Mutations

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1 c.68_69delAG</td>
<td>BRCA1 c.68_69delAG (p.Glu23Valfs*17)</td>
</tr>
<tr>
<td>BRCA1 c.5266dupC</td>
<td>BRCA1 c.5266dupC (p.Gln1756Profs*74)</td>
</tr>
<tr>
<td>BRCA2 c.5946delIT</td>
<td>BRCA2 c.5946delIT (p.Ser1982Argfs*22)</td>
</tr>
<tr>
<td>BRCA2 c.771_775delTCAAA</td>
<td>BRCA2 c.771_775delTCAAA</td>
</tr>
<tr>
<td>MSH2 c.1906G&gt;C</td>
<td>MSH2 c.1906G&gt;C (p.Ala636Pro)</td>
</tr>
<tr>
<td>MSH6 c.3959_3962delCAAG</td>
<td>MSH6 c.3959_3962delCAAG (p.Ala1320Gluufs*6)</td>
</tr>
<tr>
<td>CHEK2 c.1100delC</td>
<td>CHEK2 c.1100delC (p.Thr367Metufs*15)</td>
</tr>
<tr>
<td>CHEK2 c.1283C&gt;T</td>
<td>CHEK2 c.1283C&gt;T (p.Ser428Phe)</td>
</tr>
<tr>
<td>APC c.3920T&gt;A</td>
<td>APC c.3920T&gt;A (p.Ile1307Lys)</td>
</tr>
<tr>
<td>MUTYH c.1187G&gt;A</td>
<td>MUTYH c.1187G&gt;A (p.Gly396Asp)</td>
</tr>
<tr>
<td>MUTYH c.536A&gt;G</td>
<td>MUTYH c.536A&gt;G (p.Tyr179Cys)</td>
</tr>
<tr>
<td>NBN c.657del5</td>
<td>NBN c.657del5</td>
</tr>
<tr>
<td>FANCC c.456 + 4A&gt;T</td>
<td>FANCC c.456 + 4A&gt;T</td>
</tr>
<tr>
<td>PALB2 c.1592delT</td>
<td>PALB2 c.1592delT</td>
</tr>
<tr>
<td>CHEK2 (p.I157T)</td>
<td>CHEK2 (p.I157T) and (p.S428F)</td>
</tr>
<tr>
<td></td>
<td>Low penetrance, unclear clinical utility; does not cause polyposis</td>
</tr>
<tr>
<td></td>
<td>Biallelic MUTYH carriers have polyposis condition known as MUTYH polyposis</td>
</tr>
<tr>
<td></td>
<td>Biallelic MUTYH carriers have polyposis condition known as MUTYH polyposis</td>
</tr>
</tbody>
</table>

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possibly germline, which would warrant confirmation on a new sample type (blood, saliva) by a Clinical Laboratory Improvement Amendments—College of American Pathologists laboratory proficient in germline analysis, reporting, and interpretation.

Medical oncologists must also appreciate that the goals of somatic testing and variant interpretation are different than for germline variants. It is possible that certain tumor testing laboratories filter or computationally mask what is presumed germline.

**Tumor Testing Should Not Be Used as a Substitute When Genetic Cancer Risk Is Suspected**

Germline versus somatic laboratories have different reporting mechanisms (e.g., are missenses and/or variants of uncertain significance reported?) and different institutional knowledge. Furthermore, absence of a gene finding on a somatic testing does not equate to a negative result in the germline. As with all patients, if clinical suspicion is high for an inherited cancer predisposition syndrome, genetic evaluation and/or referral to a genetic specialist is recommended.

There is recognition that it is not feasible for busy oncology clinics to implement detailed family risk screening for every patient; furthermore, relying solely on family history has its shortcomings (e.g., inaccurate reporting, the reduced penetrance of moderate risk mutations making family history difficult to use, and stringent diagnostic and testing criteria).

If possible, it benefits the provider to be anticipatory; the likelihood of a somatic finding present in the germline is low but real. A brief discussion up front at the time of next-generation sequencing ordering can help explain the possibility of identifying inherited risk, re assurance that information will be communicated to the patient/family if determined to be relevant, and highlighting that incidentals are at times “unavoidable.” Table 3 proposes a pre- and postchecklist that could be referenced quickly to mitigate (although not eliminate) some of the current issues.

**KEY DISCUSSION POINTS FOR PATIENTS AND THEIR FAMILIES**

If a germline mutation is suspected and/or confirmed, here are some main discussion points to consider, recognizing that discussions are tailored and nuanced for each patient.

**Basic Genetic Education and Implication for the Family**

Most mutations in tumors are not inherited; rather, they develop only within cancerous cells. Germline mutations are rare but can be passed down to children and can be associated with an increased risk for cancer. In most cases, a parent who has a germline mutation has a 50/50 chance of passing down this mutation to each child. We all have an expected 7 to 10 genes (of 20,000) that do not function due to a mutation.

**Implications of Results Vary Depending on the Gene, Result, and Age and Sex of the Patient**

There are high-risk genes, moderate-risk genes, and genes for which there may be a cancer risk association but it remains unclear (Tables 4 and 5). A positive test result for a mutation does not guarantee that patients will develop cancer in their lifetime; however, this test may show a need for additional medical care to protect health. Some gene mutations cause higher risks for cancer (BRCA1/2), whereas others may confer modest increased risk (CHEK2 for breast cancer and RAD51C/D for ovarian cancer). It is important to recognize that not all gene mutations confer the same risk, and many are not yet characterized for either cancer risk or for disease biology or treatment implications. Many newly implicated rare variants have limited to no data around the relative risk of developing cancer or a therapeutic response profile. However, there are medical care guidelines and interventions for some key genes, some of which are proven to be life-saving and others more controversial. There are evidence-based recommendations in some cases, consensus guidelines in others, and no clear consensus or guidelines others. With few exceptions (TP53), most testing of this nature is recommended for individuals older than 18 years. Reproductive issues may influence decisions, especially in younger women.

**Psychosocial Assessment**

It is important to establish a mutual agenda and evaluate family dynamics. Although inherited health risk information may not directly benefit the patient’s care, the patient is the most informative individual to evaluate to see whether this finding could be inherited or passed down. Identification of an inherited gene mutation does not mean an individual has or will develop cancer; however, the risks may be higher. Conversely, testing negative for one or more inherited gene mutations does not eliminate all likelihood of developing cancer. In addition, relatives should be followed based on their own personal and family history.

It is also recommended that physicians assess the patient’s willingness to share information with relatives and to potentially establish a point of care (next of kin), as inherited cancer genetics is evolving rapidly and there could be updates in the future, especially if results are uncertain.

Individuals are adaptive and most can effectively assimilate risk information. Sometimes patients do not want to “burden” their families with genetic risk information and they feel guilty or ashamed. It is important to share with patients that most individuals, including offspring, would
feel that the benefits of having predictive health risk information outweigh the risks. Most individuals would and do prefer to take charge of their medical care if there are interventions for early detection and prevention. Finally, coping strategies differ between individuals and understanding a patient’s coping mechanism may be used to potentially clarify misinformation. Mutation carriers may experience fatalistic thoughts (e.g., that cancer is not a matter of “if” but “when” and that there is nothing to mitigate such a high risk for disease). Others may avoid addressing their risk out of fear. In “high-risk” families, individuals’ perceptions of risk and mortality are oftentimes shaped by their strong family history of disease (their family legacy). Others may choose to learn as much as possible about their risk or disease (intellectualism), insert humor, or take the “fighting spirit” approach (e.g., those motivated to avoid a similar fate). Individuals may pull from multiple strategies. By evaluating the coping strategy, providers can normalize emotions and correct misinformation and thus make navigation of health risk information and care easier.

The goal of this article is to provide a basic framework for considering somatic and germline testing, as well as the downstream familial impact of an inherited finding, it cannot fully address all of the current issues nor should this be used as a substitute when genetic specialist support is available. It is hoped that this may serve as a supplement to the knowledge gleaned from the experts positioned at both the testing laboratories and within one’s own community (Sidebar 2).

References

The Winds of Change: Emerging Therapeutics in Prostate Cancer

Carmel J. Pezaro, BHB, MBChB, FRACP, DMEEdSc, Ariel E. Marciscano, MD, PhD, and Ravi A. Madan, MD

OVERVIEW

The last decade has seen substantial advances in androgen receptor targeting in prostate cancer. In addition, advances have been made in immunotherapy and radiopharmaceutical-based therapy, although their optimal use in the clinic remains unclear. Recent understanding of the relevance and actionability of DNA damage repair mutations in a considerable minority of patients with prostate cancer is likely to open up a new frontier in prostate cancer therapeutics. As androgen receptor-directed therapy moves earlier in the disease process for prostate cancer, advances in these nonandrogen receptor-based therapeutics may take on greater significance in the years to come.

The last decade has seen important advances in prostate cancer therapeutics, including enzalutamide, abiraterone acetate, sipuleucel-T, cabazitaxel, and radium-233. Most notable are the antiandrogen strategies developed to target the mechanisms of resistance to androgen-deprivation therapy, the foundation of systemic therapy in prostate cancer. Such tumor alterations include androgen receptor (AR) overexpression and secondary production of androgens, likely by prostate cancer cells. By targeting the AR with high affinity and impacting its translocation to and function within the nucleus, enzalutamide represents a considerable advance over first-generation antiandrogens. In addition, abiraterone effectively inhibits secondary androgen biosynthesis. Both have demonstrated remarkable improvements in progression-free survival (PFS), but neither are curative. Furthermore, with mounting data supporting earlier use of these therapies, there is increasing need for new therapeutic strategies in advanced prostate cancer. PARP inhibition, radiopharmaceuticals, and immunotherapy represent three prospective fields that could revolutionize prostate cancer therapy in the next decade.

PARP INHIBITION

In the 1990s, studies of familial breast and ovarian cancer identified mutations in tumor-suppressor genes involved in DNA repair pathways, naming them BRCA1 and BRCA2. BRCA-mutated cancer cells were unable to perform homologous recombination repair (HRR) and relied on less efficient, higher risk repair pathways to combat the ongoing DNA damage that occurred during normal cellular processes. In 2005, back-to-back publications in Nature presented preclinical data demonstrating that these cells were highly sensitive to inhibition of the PARP enzyme. Single-agent PARP inhibitors entered clinical testing, initially in cohorts enriched for germline BRCA defects and then in expanded populations with phenotypic similarities, referred to as “BRCAness.” Positive phase III trials of PARP inhibition in advanced cancers now include niraparib maintenance therapy in women with platinum-sensitive ovarian, fallopian tube, and peritoneal cancers; olaparib maintenance in women with ovarian cancers and germline BRCA mutations; and olaparib monotherapy in patients with metastatic BRCA-associated breast cancers. These trials led to the U.S. Food and Drug Administration (FDA) approval of niraparib and olaparib in selected patient subgroups.

For men with prostate cancer, PARP inhibition emerged as a novel strategy with the presentation of the TOPARP trial by Mateo et al. In this adaptive-design phase II trial, 50 men with metastatic castration-resistant prostate cancer (mCRPC) received olaparib monotherapy 400 mg twice daily, until progression, toxicity, or withdrawal. The primary endpoint was a composite that included radiographic response, ≥ 50% prostate-specific antigen (PSA) decline, or CellSearch circulating tumor cell conversion. All of the enrolled men had received at least one line of chemotherapy for mCRPC, and almost all had received at least one oral AR-targeting agent. Of the 49 men evaluable for activity, 16 had a treatment response (response rate 33%; 95% CI, 20% to 48%), with median treatment duration of 40 weeks in responders and a tolerable toxicity profile. Of the responses, five represented circulating tumor cell conversion alone, with a 50% or higher PSA decline observed in the other 11 patients, accompanied by radiologic response in six patients. Most significantly, 14 of the 16 responding patients had identified cytotoxicity, but also as a monotherapy in those cancers with inbuilt genomic susceptibility, providing a combined effect termed synthetic lethality (Fig. 1). Single-agent PARP inhibitors entered clinical testing, initially in cohorts enriched for germline BRCA defects and then in expanded populations with phenotypic similarities, referred to as “BRCAness.” Positive phase III trials of PARP inhibition in advanced cancers now include niraparib maintenance therapy in women with platinum-sensitive ovarian, fallopian tube, and peritoneal cancers; olaparib maintenance in women with ovarian cancers and germline BRCA mutations; and olaparib monotherapy in patients with metastatic BRCA-associated breast cancers. These trials led to the U.S. Food and Drug Administration (FDA) approval of niraparib and olaparib in selected patient subgroups.

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DNA repair mutations, including six with germline events (BRCA2 in 3 and ATM in 3). All seven men with BCRA2 loss responded to treatment. Secondary endpoints of PFS and overall survival (OS) favored the biomarker-positive cohort.

Following the publication of TOPARP, interest in targeting DNA repair in men with prostate cancer has blossomed. If the efficacy of PARP inhibition is proven, it is likely to benefit a substantial subset of men with prostate cancer. However, our knowledge around the use of PARP inhibitors in prostate cancer must be considered to be in an infancy stage, with a plethora of unanswered questions.

Which Patient?
TOPARP enrolled men with heavily pretreated mCRPC, but it is not yet known if this represents the ideal treatment timing or optimal patient group.

**PRACTICAL APPLICATIONS**
- We review the current role of radiopharmaceuticals in prostate cancer.
- Also reviewed will be the current role of immunotherapy in prostate cancer.
- We also discuss the emerging role of PARP inhibition in prostate cancer.
- Our desire is to understand the emerging need to test patients with prostate cancer for DNA damage repair mutations.
- We detail and discuss which tests could be used when evaluating patients with prostate cancer for DNA damage repair mutations.

It has become clear that the prevalence of HRR defects in men with somatic prostate cancer is much higher than previously appreciated. In men with CRPC, the prevalence of somatic DNA repair defects has been reported to be 22.7%,\(^\text{17}\) with a higher prevalence of 33% in the TOPARP population. We do not yet have longitudinal studies of somatic HRR defects or BRCAness in prostate cancer, but these data indicate that a noteworthy proportion of men with mCRPC may develop somatic mutations sensitizing to PARP inhibition, depending on the evolving cancer behavior and any impact of tumor heterogeneity. However, although oral PARP inhibitors appear generally well tolerated in clinical trial populations, saving treatment until patients have exhausted other therapies risks a poorer ratio of therapeutic benefit to toxicity.

In a multicenter study of 150 men with metastatic prostate cancer, germline mutations in DNA repair genes were identified in 11.8%, most commonly in BRCA2, ATM, and CHEK2.\(^\text{18}\) Importantly, mutations were not adequately predicted by family history or age at diagnosis. Irrespective of prostate cancer, these germline mutations may have important implications for nonprostate cancer risk and for genetic relatives. At present, there are insufficient data to differentiate treatment responsiveness between men with germline or somatic defects or across various HRR mutations.

Although the prevalence is lower in the total population of men with early-stage prostate cancer, germline BRCA mutations have been associated with more aggressive tumor features, increased risk of metastatic spread, and shortened cancer-specific survival.\(^\text{19,20}\) Identifying men with HRR mutations promises opportunities to develop adjuvant therapies, and indeed, one phase I neoadjuvant trial is already underway (NCT02324998).

**FIGURE 1. DNA Repair and the Role of PARP Inhibitors**

A: DNA with a single strand break  
B: PARP complex binds to the broken DNA strand, to initiate repair  
C: Introduction of PARP inhibitor (yellow) traps the PARP complex at the site of damage  
D: PARP trapping stalls DNA replication and causes a double strand break (DSB). Cells deficient in HRR are unable to repair the DSBs, accumulating defects and leading to cell death.

Abbreviation: HRR, homologous recombination repair.
Which Test?
In TOPARP, all men underwent tumor biopsy during screening, with whole-exome and transcriptome studies performed on tissue as well as germline whole-exome DNA sequencing on saliva. Outside of clinical trials, however, repeated biopsy remains a challenging proposition for many patients and clinicians. Using archival specimens enables wider testing, but risks missing the evolution of somatic mutations. At present, techniques to identify somatic mutations in peripheral blood remain investigational. In contrast, germline testing with targeted sequencing using DNA from saliva, buccal cells, or peripheral blood is well established. Although we may look to colleagues in other solid tumors to learn about HRR testing, each cancer has unique attributes of natural history, platinum exposure/response, and BRCA1/2 that may necessitate different strategies to identify patients. Ongoing clinical trials will enroll men with defects in a broad panel of HRR genes and are expected to provide invaluable data from screening as well as treatment phases, including further population-level data on mutation frequencies.

Of concern, traditional models that mandate genetic counseling prior to testing are ill equipped to deal with the influx of patients with prostate cancer. Recent cross-sectional survey data suggested that fewer than 20% of women with breast or ovarian cancer in the United States have undergone genetic testing, and yet services are already stretched. Novel mechanisms for education and testing will be required to adequately service the large population of men with prostate cancer.

Which Therapy?
There are a number of PARP inhibitors in clinical development, with differing potency in trapping PARP. The clinical relevance of this pharmacologic variation is unknown. At present, men with metastatic prostate cancer and DNA repair defects are being enrolled to multiple phase II and phase III trials (Table 1). Although this multiplicity of trials has likely slowed enrollment among this relatively less common cancer subtype, men currently have easy access to genomic testing and research participation worldwide.

PARP inhibitors are predicted to be tolerable in combination. The results of a phase II trial combining veliparib with abiraterone and prednisone (NCT01576172) are awaited. Upcoming studies will combine PARP inhibitors with a number of prostate cancer–directed, targeted, and immune therapies (Table 1).

Already in breast and ovarian cancer research, a number of mechanisms of induced resistance to PARP inhibition have been described. It is likely that there will be overlapping mechanisms in prostate cancer, and further research is expected.

There is always a tension between fulfilling research requirements and expediting access to novel treatments for patients in need. Although PARP inhibitors represent a compelling novel mechanism of action, their efficacy in advanced prostate cancer has not yet been solidified. The value of high-quality translational research to correctly develop and disseminate treatment to the optimum patient group cannot be overstated.
that concomitant antiandrogen therapy (abiraterone, enzalutamide, or both) and Ra-223 could potentially be safely combined and further extend median survival for patients with mCRPC, including those who are asymptomatic.\textsuperscript{27} This favorable survival and safety profile was further corroborated by the phase II U.S. expanded access program as well as the eRADicAte study, which demonstrated that the combination of Ra-223 and abiraterone resulted in a clinically meaningful improvement in quality of life and pain metrics without the addition of new or concerning safety signals.\textsuperscript{28,29} These encouraging clinical experiences laid the foundation for the double-blind phase III ERA 223 study (NCT02043678).

This study randomized chemotherapy-naive patients with asymptomatic/minimally symptomatic bone-predominant mCRPC in 1:1 fashion (806 patients) to abiraterone (plus prednisone/prednisolone) with or without Ra-223 to test whether the addition of Ra-223 would increase symptomatic skeletal-related event–free survival. Unfortunately, more fractures and deaths have been observed in the experimental Ra-223/abiraterone arm, prompting Bayer to prematurely unblind this trial to evaluate the safety concerns raised by the Independent Data Monitoring Committee.\textsuperscript{30}

### TABLE 1. Active Phase II to III Trials of PARP Inhibitors in Men With Prostate Cancer and DNA-Repair Abnormalities

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Drug</th>
<th>ClinicalTrials.gov Identification Number; Trial Name</th>
<th>Phase; Study Size</th>
<th>Setting; Comparator (If Applicable)</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase II in CRPC</td>
<td>Olaparib (completed)</td>
<td>NCT01682772; II; 89 patients (maximum; adaptive design)</td>
<td>mCRPC, post 1 to 2 taxane chemotherapy agent(s)</td>
<td>RR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Niraparib</td>
<td>NCT02854436; Galahad</td>
<td>II; 160 patients</td>
<td>mCRPC, post 1+ chemotherapy and 1+ AR-targeting agent(s)</td>
<td>ORR</td>
</tr>
<tr>
<td></td>
<td>Rucaparib</td>
<td>NCT02952534; TRITON2</td>
<td>II; 160 patients</td>
<td>mCRPC, post 1+ chemotherapy and 1 to 2 AR-targeting agent(s)</td>
<td>ORR + PSA response</td>
</tr>
<tr>
<td></td>
<td>Talazoparib</td>
<td>NCT03148795</td>
<td>II; 100 patients</td>
<td>mCRPC, post 1 to 2 chemotherapy and 1+ AR-targeting agent(s)</td>
<td>ORR</td>
</tr>
<tr>
<td></td>
<td>Olaparib</td>
<td>NCT03263650</td>
<td>II randomized; 96 patients</td>
<td>mCRPC with aggressive characteristics; maintenance following six cycles cabazitaxel plus cabroplatin; randomized to olaparib vs. observation</td>
<td>PFS</td>
</tr>
<tr>
<td>Phase II in HSPC</td>
<td>Olaparib</td>
<td>NCT03047135</td>
<td>II; 50 patients</td>
<td>Biochemical recurrence post-RP; PSA doubling ≤6 months</td>
<td>PSA response</td>
</tr>
<tr>
<td></td>
<td>Rucaparib</td>
<td>NCT03413995; TRIUMPH</td>
<td>II; 30 patients</td>
<td>mHSPC, not on ADT</td>
<td>PSA response</td>
</tr>
<tr>
<td>Phase III in CRPC</td>
<td>Olaparib</td>
<td>NCT02987543; PROfound</td>
<td>III; 340 patients</td>
<td>mCRPC, post 1+ AR-targeting agent(s); vs. investigator choice (AA, enzalutamide, or docetaxel)</td>
<td>rPFS</td>
</tr>
<tr>
<td></td>
<td>Rucaparib</td>
<td>NCT02979534; TRITON3</td>
<td>III; 400 patients</td>
<td>mCRPC, chemotherapy-naive; vs. investigator choice (AA, enzalutamide, or docetaxel)</td>
<td>rPFS</td>
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<tr>
<td></td>
<td>Talazoparib</td>
<td>NCT03395197; TALAPRO-3</td>
<td>III; 444 patients</td>
<td>mCRPC, chemotherapy-naive; vs. investigator choice (AA, enzalutamide, or docetaxel)</td>
<td>rPFS</td>
</tr>
<tr>
<td>Combination</td>
<td>Veliparib</td>
<td>NCT01576172</td>
<td>II randomized; 148 patients</td>
<td>mCRPC, prior chemotherapy allowed; randomized to AA with or without veliparib</td>
<td>PSA response</td>
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<tr>
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<td>Olaparib</td>
<td>NCT01972217</td>
<td>II randomized; 159 patients</td>
<td>mCRPC, post docetaxel; randomized to AA with or without olaparib</td>
<td>rPFS</td>
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<tr>
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<td>Olaparib</td>
<td>NCT02893917</td>
<td>II randomized; 90 patients</td>
<td>mCRPC, post 1+ therapy for CRPC; randomized to olaparib with or without cediranib</td>
<td>rPFS</td>
</tr>
<tr>
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<td>Olaparib</td>
<td>NCT03317392</td>
<td>II/II randomized; 112 patients</td>
<td>mCRPC with bone metastases; randomized to Ra-223 with or without olaparib</td>
<td>(Phase II) rPFS</td>
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<td>NCT03012321</td>
<td>II randomized; 70 patients</td>
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<td>II randomized; 300 patients</td>
<td>mCRPC, prior chemotherapy allowed; randomized to nivolumab plus one of: rucaparib, docetaxel, or enzalutamide</td>
<td>ORR plus PSA response</td>
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<tr>
<td></td>
<td>Talazoparib</td>
<td>NCT03395197; TALAPRO-3</td>
<td>III; 444 patients</td>
<td>mCRPC, chemotherapy-naive; randomized to AR-targeting agent with or without talazoparib</td>
<td>rPFS</td>
</tr>
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</table>

**Abbreviations:** AA, abiraterone acetate (in combination with corticosteroid); ADT, androgen-deprivation therapy; HSPC, hormone-sensitive prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; DRR, overall response rate; RP, radical prostatectomy; rPFS, radiographic PFS; RR, response rate.

**Based on trials listed on ClinicalTrials.gov as of January 31, 2018.** AR-targeting agents include abiraterone, enzalutamide, or similar.
This is somewhat unexpected, as prior studies have not indicated that this combination yields excessive toxicity, and Ra-223 monotherapy continues to be well-tolerated in the long-term follow-up of the ALSYMPCA cohort.\textsuperscript{27-29,31} Further analysis is required to understand if there is some form of synergy with toxicity among Ra-223, abiraterone, and/or prednisone. The jury is currently still out as to whether antiandrogens and Ra-223 form a safe and efficacious partnership in prostate cancer; however, the ERA 223 study underscores the importance of phase III trials and serves as a reminder that promising combination regimens can be detailed by an adverse risk-benefit profile. Based on current data, the use of abiraterone and prednisone with Ra-223 cannot be recommended.

PSMA-directed radioligand therapy (RLT) has rapidly emerged as an intriguing therapeutic option for mCRPC. Compared with calcium-mimetic/bone-targeting Ra-223, which addresses osseous metastases, PSMA-directed RLT holds the distinct advantage of potentially addressing both visceral and bony micro- and macroscopic disease. Owing to high surface expression on malignant prostate carcinoma cells, multiple PSMA-targeted antibodies and small molecules are being evaluated both preclinically and clinically. Among these agents, the beta-emitting radioconjugate \textsuperscript{177}Lu-PSMA is the most commonly used PSMA-specific RPT in the clinic. Indeed, the DOTA-conjugated radioligand, \textsuperscript{177}Lu-PSMA-617, has demonstrated favorable biodistribution and pharmacokinetic properties possessing high target affinity, prolonged intratumoral retention, and minimal renal uptake.\textsuperscript{32} Although highly specific PSMA binding is feasible, and current experience suggests that this approach is well-tolerated, it is important to acknowledge that PSMA is not exclusively expressed on tumor cells, and the off-target effects of PSMA-directed RLT could result in potentially serious and/or irreversible injury to the kidneys and salivary glands as well as other radiosensitive normal tissues.\textsuperscript{33,34} As such, rigorous radiation dosimetry and prospective clinical evaluation are desperately needed to validate the safety and efficacy of this approach. Despite these concerns, nascent clinical experiences have been quite promising and appear to offer benefit to some patients with mCRPC with disease that is refractory to multiple prior lines of therapy.

Although there is a paucity of prospective, randomized clinical data and limited long-term follow-up, compelling retrospective data have emerged from several centers in Germany, which have led the charge of PSMA-directed RLT into the clinic. Similar to Ra-223, the German experience suggests that PSMA-RLT improves survival in addition to palliating symptomatic disease. This is particularly notable, as several retrospective series have observed a survival benefit among heavily pretreated cohorts of patients with mCRPC who have previously been exposed to chemotherapy, enzalutamide, abiraterone, or Ra-223.\textsuperscript{34-36} To better understand factors that determine the clinical benefit of \textsuperscript{177}Lu-PSMA-617 RLT, recent work by Rahbar et al\textsuperscript{37} reported that PSA decline (approximately \( \geq 20\% \)) following the first RLT treatment, pretreatment alkaline phosphatase less than 200 U/L, and cumulative injected activity greater than 18.8 GBq were associated with longer survival in a cohort of 104 patients with mCRPC undergoing treatment with 351 cycles of RLT (administered every 8 weeks until progression, death, or toxicity). An independent retrospective analysis exploring a similar population of patients (100 patients receiving 347 cycles of RLT) confirmed that biochemical response (approximate PSA decline \( \geq 14\% \)) as well as lack of hepatic involvement were predictive of OS.\textsuperscript{38} In addition to identifying clinically relevant prognostic and predictive biomarkers for PSMA-directed RLT, the emergence of PET-based PSMA-specific molecular imaging is an increasingly useful tool for diagnosis, patient selection, and monitoring of RLT treatment response and will undoubtedly shape future clinical management.\textsuperscript{39}

Much work is needed to determine the optimal dose regimen/schedule and to verify the perceived safety and survival benefit of \textsuperscript{177}Lu-PSMA-617 RLT. There are now two prospective studies in the United States that are actively enrolling patients with advanced mCRPC and will provide valuable information over the coming years.\textsuperscript{40} A phase I dose-escalation study (NCT03042468) led by Weill Cornell Medicine will investigate the dose-limiting toxicity of fractionated \textsuperscript{177}Lu-PSMA-617 (three-plus-three design with six dose levels) and cumulative maximum tolerated dose (cumulative dose range 3.7 GBq to 22.2 GBq) to inform future phase II studies. Additionally, a multicenter phase II trial (NCT03042312) will evaluate PSA decline of 50\% or more at 12 weeks as a surrogate for efficacy at two different dose levels (6.0 GBq vs. 7.4 GBq). Internationally, the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group has begun enrollment to a randomized phase II trial, comparing to cabazitaxel (ANZUP1603). In the next 5 years, we will learn if these exciting signals will become a genuine treatment consideration alongside or in conjunction with several other recently FDA-approved agents. Given the theoretical advantages of alpha-particle therapy, PSMA-targeted alpha-particle RLT (i.e., \textsuperscript{212}At and \textsuperscript{225}Ac) might prove to be more effective, although nephrotoxicity and other late effects remain an ongoing concern.\textsuperscript{41}

Cautious optimism is warranted for RPT in prostate cancer. Ra-223 and PSMA-targeted RLT have the potential to transform the therapeutic landscape for men with advanced prostate cancer—their unique mechanism of action and nonoverlapping toxicity profiles suggest that combination strategies and their use in earlier stages of disease might further improve outcomes.

**Immunotherapy**

Modern immunotherapy in clinical oncology arguably made its debut in prostate cancer in 2010 when sipuleucel-T, a therapeutic vaccine derived from a patient’s own immune cells collected via apheresis, demonstrated an OS advantage in two phase III trials.\textsuperscript{42,43} Despite a statistically significant and clinically meaningful improvement in OS (25.8 vs. 21.7 months; HR 0.78; 95\% CI, 0.61 to 0.98; \( p = .03 \)), clinicians were reluctant to use a treatment that had no immediate
changes in short-term disease progression (within 3 months) or rare impact on PSA. To this day, the treatment remains a potentially polarizing topic among prostate cancer clinicians despite trials demonstrating immunologic impact of the treatment and the potential for sipuleucel-T to drive T cells to the tumor microenvironment. In the years to come, however, such attributes of immune activation could make therapies targeting immune checkpoints more effective in prostate cancer.

In recent years, five new therapies have demonstrated an ability to improve survival in prostate cancer; conspicuous by their absence are the immune checkpoint inhibitors that have revolutionized the treatment landscape in other cancers including melanoma, non–small cell lung cancer, and bladder cancer. Two trials using ipilimumab (anti–CTLA-4; FDA approved in melanoma) in advanced prostate cancer failed to improve survival. Meanwhile, anti–PD-1/PD-L1 inhibitors have had very modest impact as monotherapy in prostate cancer, corroborating data that suggest the vast majority of prostate tumors are PD-L1 negative. The one subset of patients who do benefit from anti–PD-1/PD-L1 therapy are patients with microsatellite instability high tumors, who make up approximately 2% to 5% of all patients with advanced prostate cancer, potentially compelling clinicians to test patients for this targetable defect.

The assessments of the root cause of the relative ineffectiveness of immunotherapy in prostate cancer is similar to other tumor types that do not respond to PD-1/PD-L1 inhibition. The lack of immune cells in the tumor microenvironment (i.e., an immunologically “cold” tumor microenvironment) is the most likely explanation for the lack of benefit seen with PD-1/PD-L1 inhibitors. To have an effect, these treatments must disrupt the molecular engagement of PD-1 and PD-L1 in the tumor microenvironment that essentially allows tumor or stroma in the microenvironment to abrogate immune cell function. If there are immune cells present, PD-1/PD-L1 inhibitors essentially free them from immunologic inanimation, allowing them to recognize and kill cancer cells, hence the rapid and remarkable antitumor responses seen in patients with PD-1/PD-L1 inhibitors. To have an effect, these treatments must disrupt the molecular engagement of PD-1 and PD-L1 in the tumor microenvironment that essentially allows tumor or stroma in the microenvironment to abrogate immune cell function. If there are immune cells present, PD-1/PD-L1 inhibitors essentially free them from immunologic inanimation, allowing them to recognize and kill cancer cells, hence the rapid and remarkable antitumor responses seen in patients with PD-1/PD-L1 inhibitors. If, however, the tumor is immunologically cold, then the tumor microenvironment is devoid of immune cells, and PD-1/PD-L1 inhibitors are shooting molecular blanks, rendering them ineffective.

With that understanding, strategies are being developed to modify the potentially dynamic immune microenvironments of cold tumors in an effort to heat them up immunologically with immune infiltration. As mentioned earlier, therapeutic cancer vaccines have the potential to increase immune cell targeting of the tumor microenvironment. A study of sipuleucel-T in the neoadjuvant setting prior to radical prostatectomy demonstrated the ability to increase active T-cell infiltration of the prostate after 1 month of therapy. Multiple trials are currently underway with vaccines and checkpoint inhibition in prostate cancer. Pembrolizumab, which heretofore has demonstrated little activity as monotherapy, is being combined with a DNA-based vaccine targeting prostatic acid phosphatase. This study, which is also evaluating the optimal sequence of therapy, has produced preliminary data indicating potential for the combination when given concurrently to induce PSA declines and radiographic responses in mCRPC, neither of which would be expected with either treatment alone. This study is ongoing. Two additional trials are combining vaccines and immune checkpoint inhibition in earlier stages of the disease. One trial will combine nivolumab and the therapeutic cancer vaccine prostvac (pox viral-based targeting PSA) in the neoadjuvant setting (NCT02933255). Another trial will combine two pox viral–based vaccines, prostvac and CV-301 (targets MUC1 and CEA), with M7824, a PD-L1 inhibitor that also has the function to bind/deplete transforming growth factor-β (an immune suppressive cytokine) in the tumor microenvironment (NCT03315871). Both of the latter two studies are currently accruing at the National Cancer Institute. Antiandrogen therapies are at the forefront of treatment of mCRPC, and there are studies ongoing combining these agents with immune checkpoint inhibition. At the leading edge of these studies is a trial combining enzalutamide with pembrolizumab in mCRPC. Pembrolizumab is added to patients who are progressing on enzalutamide. Based on preliminary data, responses in approximately 20% of patients have been reported, higher than would be expected with pembrolizumab alone. There are existing data that have suggested the enzalutamide can have immune-stimulatory effects in patients with prostate cancer. Furthermore, data from circulating immune cells in patients being treated with enzalutamide have indicated that there is increased PD-1 expression on the cells, thereby demonstrating the potential for synergistic therapy. The clinical trial combining enzalutamide with pembrolizumab is ongoing, and further enrollment will define the potential of this combination.

There is also growing interest in combining immunotherapy with emerging therapeutics such as radiopharmaceuticals and PARP inhibitors in prostate cancers, agents with established or burgeoning roles in prostate cancer as described previously. Radiation has been shown to enhance immune recognition of cancer cells via a process known as immunogenic modulation by which cancer cells that are not euthanized by radiation directly can be modified at the level of the cell surface. These changes lead to increased expression of molecules such as tumor-associated antigens, major histocompatibility complex class I molecules that can augment immune recognition of tumor cells, ultimately potentiating immune cell killing. Sublethal levels of radiation can also lead to upregulation of molecules such as FAS, which can be engaged by immune cells in the tumor microenvironment as a mechanism for cell killing. Although the immune potential of radiation was initially described in conjunction with external beam radiation, similar effects have been demonstrated using alpha- and beta-emitting radiopharmaceuticals. Indeed, a previous clinical trial has suggested improved clinical benefit when beta-emitting 153Sm was combined with the therapeutic cancer vaccine prostvac, compared with 153Sm alone. Building on this strategy, there

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are ongoing trials combining immunotherapy (sipuleucel-T and PD-1/PD-L1 inhibitors) with Ra-223.

As mentioned previously, PARP inhibition is relevant based on the genomics of up to a third of patients with prostate cancer; however, multiple trials are attempting to exploit hypothesized immunologic synergies. In addition, hypotheses suggest the possibility that DNA damage induced by PARP inhibition in cancer cells can increase the amount of DNA in the cytosol, thereby trigging the STING pathway. Once activated, the STING pathway, likely an innate defense mechanism against viral infection, leads to increased production of interferon with the tumor microenvironment, thereby both activating a local immune response and upregulating PD-L1 expression. Yet another hypothesis suggests that DNA damage induced by PARP inhibition can increase mutational burden within a tumor, thereby making it a more attractive immunologic target and thus more likely to express PD-L1. Although the rationale remains empirical at this point, multiple trials are evaluating this combination with some preliminary evidence of activity in a small number of patients. One expanded cohort of a current trial is evaluating prostate cancer specifically based on preliminary data from the first 17 patients. The early findings suggest that the combination of olaparib and durvalumab may be more effective than olaparib alone in patients with DNA damage repair mutations and may even bring benefit to those without known mutations in the targeted pathway.

Again, additional data will be required to validate the initial enthusiasm for this combination in prostate cancer.

CONCLUSION

From the emergence of docetaxel for mCRPC in 2004, through the development of next-generation androgens, additional chemotherapy agents, and RPT, great strides have been made in systemic therapy for advanced prostate cancer. Nonetheless, curing metastatic prostate cancer remains an elusive goal. Additional therapies will be required to further enhance options for men with advanced prostate cancer. Emerging targets for treatment of this disease now include DNA damage repair mutations and microsatellite instability high status, which can be impacted by PARP inhibition and PD-1/PD-L1 inhibition, respectively. Furthermore, targeting the bone microenvironment, the primary reservoir for disease for the vast majority of men with mCRPC, is a strategy that has not yet been fully exploited, but emerging RPT and RLT options hold promise. Appropriately combining and sequencing these new therapies within the existing treatment paradigm will also require further clinical investigation. Perhaps data from the trials currently ongoing with PARP inhibitors, RPT/RLT, and immunotherapy will highlight the path forward for treating advanced prostate cancer and move the field one step closer to its ultimate goal: to limit morbidity and mortality for patients diagnosed with prostate cancer.

References


GERIATRIC ONCOLOGY
Global demographic changes in the coming decades will have profound implications for public health, health care spending, and medical research. One of the most acute demographic changes on the horizon is the overall aging of the population. The population of older adults is growing, with a worldwide projected average annual increase of 27.1 million from 2015 to 2050.1 As cancer is a disease of aging, quality cancer care for older adults is imperative. However, there is limited evidence for treating this complex and often vulnerable population. In particular, older adults are under-represented on both cooperative group and U.S. Food and Drug Administration (FDA) registration studies that set the standard for oncology care.2-4 Hence, older adults are often treated using evidence developed in younger, healthier, cohorts.5

Several efforts have been underway by various stakeholders to address this critical need to improve the evidence base for treating older adults with cancer, including the National Institute on Aging, National Cancer Institute (NCI), Cancer and Aging Research Group, Institute of Medicine (IOM), ASCO, and the FDA. In this manuscript, we summarize these efforts and propose recommendations to fill knowledge gaps pertaining to the treatment of older adults with cancer.

U13 CONFERENCES
From September 2010 to May 2015, the Cancer and Aging Research Group, in collaboration with the NCI and National Institute on Aging, convened three U13 conferences. The overall aim of the conference series was to discuss the current level of research evidence in geriatric oncology, outline knowledge gaps, and propose strategies for research designs that would address these gaps in 10 years. At the first conference, “Biological, Clinical, and Psychosocial Correlates at the Interface of Aging and Cancer Research,” recommendations were put forth for inclusion of a geriatric assessment (GA) in clinical trials, and the following recommendations were made: (1) the incorporation of GA into oncology research, (2) consistent incorporation of physiologic and biologic markers of aging in oncology trials, (3) increased studies of vulnerable older adults and/or those age 75 and older, and (4) the incorporation of specific age-associated support in research infrastructure.5

The second conference, held in 2012, “Design and Implementation of Therapeutic Clinical Trials for Older and/ or Frail Adults with Cancer,” focused on the design of therapeutic clinical trials for older and frail adults with cancer and, in a subsequent white paper, offered recommendations...
for improving accrual of older adults to clinical trials. “To increase the enrollment of older adults onto clinical trials” the authors wrote, “clinical trials must be developed specifically for those individuals who do not meet the eligibility criteria or are not fit enough for enrollment onto clinical trials focused on individuals of all ages.” Conference topics included geriatric and quality-of-life (QOL) endpoints for clinical trials in older adults and statistical considerations in those novel endpoints such as the impact of therapy on function and cognition.

The third and final U13 conference, held in May 2015, focused on developing and implementing intervention studies to improve the quality of survival in older and/or frail adults with cancer. These include designing intervention studies with outcomes meaningful for older adults, such as functional independence. Recommendations included that future intervention trials for older adults with cancer should: (1) rigorously test interventions to prevent the decline of or improve health status, especially interventions focused on optimizing physical performance, nutritional status, and cognition while undergoing cancer treatment; (2) use standardized care plans based on GA findings to guide targeted interventions; and (3) incorporate the principles of geriatrics into survivorship care plans.

IOM REPORT

In its 2013 report on the quality of cancer care in the United States, the IOM identified a crisis in cancer-care delivery. Generally, it identified the need for “high-quality, evidence-based strategies to guide cancer care and ensure efficient and effective use of scarce resources.” More specifically, much of this identified crisis is rooted in how cancer care is delivered to older patients. The report notes that the current infrastructure is “not prepared to take care of this growing cancer population, as few of [its] standard treatment approaches have been evaluated in this setting.” This concern especially applies to older adults with multiple chronic diseases (comorbidity). The report recommends an expansion of the breadth of data collected on cancer interventions for older adults to optimize treatment decision-making for this population.

Furthermore, the IOM report identified workforce issues related to the care of older adults with cancer. It says that the “growth in absolute numbers of older adults is likely to result in a greater total volume of patients with cancer and a greater need for service than the current workforce can provide.” The report endorsed the recommendation of a previous IOM report, which supports the enhancement of the geriatric competency of the general health care workforce.

ASCO RECOMMENDATIONS

In response to the 2013 IOM report, the ASCO convened a subcommittee of the Cancer Research Committee to develop recommendations for improving the evidence base for older adults with cancer. The committee identified five recommendations in a 2015 article: researchers should: (1) use clinical trials to improve the evidence base for treating older adults with cancer; (2) leverage research designs and infrastructure for generating evidence on older adults with cancer; (3) increase FDA authority to incentivize and require research involving older adults with cancer; (4) increase clinicians’ recruitment of older adults with cancer to clinical trials; and (5) use journal policies to improve researchers’ reporting on the age distribution and health risk profiles of research participants. The article includes action items for each recommendation, recommendation goals, and opportunities in geriatric oncology clinical trial designs. Specifically, the ASCO report recommends, among other things, that the authority of the FDA be increased to incentivize and require research that includes older adults. To this point, the report endorses three action items: (1) Congress should provide the FDA authority to require that a drug or biologic marketing application contain a plan to gather data and develop recommendations on safety, efficacy, and dosing in older adults; (2) Congress should grant the FDA authority to create incentives for companies that conduct clinical trials of new cancer treatments in older adults; and (3) the FDA should include experts in aging and geriatric oncology on its advisory boards to provide scientific advice on the development and assessment of novel agents and emerging federal policies.

FDA WORKSHOP

In November 2017, ASCO and the FDA held a public workshop for geriatric oncology to discuss the issues highlighted by the IOM and the recommendations from ASCO. According to the IOM, the FDA has issued guidance, but not requirements, that include (1) “the routine and thorough evaluation of the effects of drugs on older adults”; (2) the guidance that clinical studies should comprise a population that reflects the patients that will receive the drug after it is marketed; and (3) the inclusion of individuals older than age 75 in clinical trials. Nevertheless, in 2013, Scher and Hurria noted that despite comprising 59% of the population with chronic diseases (comorbidity), the report recommends an expansion of the breadth of data collected on cancer interventions for older adults to optimize treatment decision-making for this population.
cancer, adults 65 and older were only 33% of trial participants in the geriatric usage sections of the drug package insert for 24 drugs approved for cancer treatments between 2007 and 2010. Participants at the Geriatric Oncology Workshop included experts from the fields of cancer and aging, representatives from the FDA, NCI, industry, Centers for Medicare & Medicaid Services, European Medical Association, and patient advocates. The workshop was organized into thematic sessions each designed to address specific topic areas critical to increasing the evidence base for older adults. Highlights and next steps will be discussed in the remainder of this review.

**Designing Clinical Trials for Older Adults With Cancer**

Improving the evidence base for older adults with cancer requires the design of trials that both facilitate the enrollment of representative older patients and capture comprehensive data that can best inform individualized management strategies. Key questions for older and frail adults with cancer include whether established treatments are equally tolerable and efficacious and how to evaluate novel therapeutic strategies in these populations. Designing trials accounting for both the heterogeneity of aging and a broader range of outcomes relevant to older adults is challenging.

Randomized controlled trials enrolling representative older adults are critical to inform evidence-based practice. Clinical trials designed specifically for older adults can be an optimal vehicle to establish standards of care particularly for those adults who are not routinely represented in registration trials (i.e., older than age 75, multiple chronic conditions, or frail). Another important role for randomized controlled trials is testing novel treatment allocation strategies accounting for frailty that will help individualize care. For example, Corre et al randomly assigned older patients with lung cancer to usual care versus GA-directed therapy and demonstrated equivalent survival but decreased toxicity in the GA-directed arm. This type of study can inform novel strategies to individually allocate treatment plans based on GA results. Although randomized trials remain the gold standard, they often require large sample sizes and considerable resources. Hence, thoughtful and efficient use of varied types of trials will be necessary to both enroll and optimally address questions relevant for older patients.

Prospective cohort studies can augment the evidence base, providing information on topics ranging from patterns of care, decision-making, treatment effectiveness, toxicity, and risk prediction. Results of well-designed cohort studies can translate directly into practice-changing management. These trials are particularly suited to the study of patients with multiple chronic conditions and frailty. Examples include cohort studies demonstrating the utility of using GA to predict chemotherapy toxicity among older patients receiving chemotherapy. Furthermore, embedded correlative studies provide a resource-efficient strategy to gather information in the context of a planned clinical trial that can better characterize older patients to inform generalizability and subset analyses, develop risk prediction models, and collect longitudinal outcome data (i.e., functional outcomes) related to treatment tolerance and QOL. Smaller single-arm and early-phase trials are particularly important to evaluate treatment efficacy in older adult populations and better understand the implications of age-related changes in pharmacokinetics/pharmacodynamics.

Novel trial strategies also warrant consideration. Extended trial designs (i.e., including the addition of an older cohort to the superior arm in a randomized study) could efficiently use existing infrastructure to evaluate treatment tolerability among older patients and those with comorbidity. Another novel approach proposed in the workshop is the incorporation of a concurrent additional observational arm to a phase III trial that specifically focuses on accruing an adequate number of older adults (or those who are frail or have specific comorbid conditions) so that the efficacy and toxicity data are captured concurrently in a more generalizable population of patients. This approach would provide timely information to practitioners and could appeal to sponsors by collecting data in parallel with the randomized controlled trials to support broader labeling indications.

Another key topic relates to the expansion of trial outcomes beyond disease-specific endpoints and survival. The impact of cancer and its treatments on outcomes such as physical function, cognition, functional independence, and global QOL is highly relevant to older adults. Similarly, the development of prefrailty or frailty could be considered as a key outcome in clinical trials. These outcomes are of concern to patients, yet we have sparse data to inform the risks and benefits related to these aspects of the treatment experience and subsequent survivorship. In a review of 127 palliative chemotherapy trials for older adults, data specific to physical function, health care use, cognitive function, and QOL were collected in 6%, 3%, 6%, and 31%, respectively. Similarly, in a review of over 1,000 hematologic malignancy phase I to III trials in the National Institutes of Health (NIH) registry, the outcomes of QOL, health care use, and function were reported in less than 10% of all studies. In considering the use of trial designs specifically for older adults, the use of composite endpoints as detailed by Wildiers et al is particularly attractive. Composite endpoints provide a multidimensional perspective of overall treatment utility. This approach can incorporate multiple well-defined patient-centric outcomes versus a combination of both the patient and provider perspectives of the treatment experience, as demonstrated in the FOCUS2 trial for older adults with advanced colorectal cancer.

Next steps were proposed during the workshop for advancing the evidence base for older adults related to trial design. Recommendations are to: (1) design trials with an additional arm for registration data specific to older and/or frail patients; (2) incorporate pharmacokinetic and genomic studies for older adults into early-phase clinical trials; (3) include patient-centric outcomes such as functional measures and QOL into phase III and postmarketing studies; (4) develop reproducible composite endpoints to capture efficacy, safety, and tolerability that meet regulatory standards;
and (5) facilitate discussion between sponsors and the FDA early in the drug-development process that addresses trial design and endpoints relevant to older adults.

**Increasing Enrollment of Older Adults in Registration Trials**

Patients enrolled in registration trials are not adequately representative of those seen in clinical practice. Trial participants are generally younger and healthier, resulting in uncertainty regarding optimal management for a large proportion of the population. There is a particular lack of data to provide an evidence-based standard of care for patients older than age 75 and those with comorbidity or frailty. Concern regarding provision of representative data on clinical trials is not limited to oncology. The NIH recently announced the Inclusion Across the Lifespan Policy to ensure that the evidence collected in NIH-funded research is applicable to those who are affected by the disease or condition being studied. Starting in 2019, NIH research applications involving human subjects will be required to describe how participants across the lifespan will be included, with justification of proposed participant age ranges. This policy reflects a key theme echoed during the workshop highlighting the importance of intentional planning to recruit patients of representative ages so that the evidence gained in clinical trials would be readily generalizable to the majority of patients with the condition studied.

Specific to oncology, the workshop addressed barriers and facilitators to enrollment of representative older adults. A key topic addressed was the ongoing effort to modernize trial eligibility criteria. A review of eligibility criteria requirements for cancer clinical trials conducted by the FDA shows that the criteria narrowly define the study population and often represent lower-risk patients. This has important implications for older adults. A recent publication by a working group established by ASCO and the Friends of Cancer Research details specific recommendations for expanding eligibility criteria related to organ dysfunction, concurrent malignancy, and comorbidities. Several commonly applied eligibility criteria were examined, including requirements for creatinine clearance higher than 60 mL/min, adequate liver function tests, absence of cardiac disease (i.e., ejection fraction more than 50% and no history of myocardial infarction), and no prior malignancy in the past 5 years. These criteria are often applied without direct relevance to the drug being tested. The working group explored the implications of these criteria for recruitment of representative patients. Using data from over 10,000 patients in the Kaiser Permanente database, the authors demonstrated the impact of applying these criteria to patients with varied cancer types. In particular, a requirement of a creatinine clearance 60 mL/min or higher among patients with breast, colorectal, lung, and bladder cancer would exclude 15%, 18%, 20%, and 34% of patients, respectively. Based on these data, the authors estimated that exclusion of patients with creatinine clearance less than 60 mL/min would preclude 20% to 46% of patients from participating in clinical trials. A large proportion of those excluded would be in the older age range (older than age 75). The article details specific recommendations for updated eligibility criteria to maintain safety and maximize trial participation. For example, if renal toxicity and clearance are not a treatment-related concern, a lower creatinine clearance (> 30 mL/min) should be applied. In addition to updated recommendations for organ dysfunction–specific criteria, the authors advocate for inclusion of measures of patient functional status that better assess fitness versus frailty in a given treatment context. Careful consideration of inclusion criteria by investigators and regulators early in trial development can ensure an increased number and diversity of patients better reflective of those who will be treated in the community.

Although refining eligibility criteria is expected to have a notable impact on trial participation, other factors beyond eligibility can influence recruitment to clinical trials. Some of these barriers are logistical challenges. For example, clinical trials frequently require additional study visits, which can be a hardship for older adults who may rely on others for transportation. Geographic barriers more broadly may influence recruitment, as a large proportion of oncologists and subsequently large clinical trials are clustered in specific states, frequently favoring access to patients living in population-dense locations. Addressing ease of access, distance traveled, and number of study visits intentionally in trial design and support infrastructure may increase access and raise the appeal of clinical trial participation to older and frail adults. Additional logistical barriers may influence providers’ recommendations for older adults to participate in trials. Recruiting older adults to clinical trials is a time-consuming process and can pose increased risk due to a higher probability of adverse events as well as a higher potential for protocol violations given a higher prevalence of conditions (i.e., comorbidities, impaired social support, polypharmacy, cognitive impairment, and functional impairment), which can impact adherence to protocol requirements. The extent to which these concerns influence providers’ recommendations for trials is unknown and warrants further attention.

Bias remains a potential barrier to trial recruitment from the standpoint of patients and providers. Consideration of the patient’s perspective, inclusive of the unique needs and priorities of older patients with cancer is critical to optimize trial design and facilitate communication strategies related to recruitment. Studies suggest that older patients with cancer report willingness to participate in cancer clinical trials. However, a disconnect between the trial design and the patient’s needs and priorities can result in lower enrollment. Engagement of patient advocates and investigators with expertise in working with varied social and demographic groups early in trial design and during implementation could overcome some of these barriers. Provider bias also warrants attention, as a common reason reported for lack of enrollment is that the provider did not recommend the trial. Research and education focused on the perspectives of patients and providers can inform strategies.
to enhance patient recruitment to trials representative of those with the disease.

Several concrete next steps were proposed to improve recruitment of representative older adults to clinical trials. There is an overarching need to harmonize efforts currently underway by multiple stakeholders including the NCI, FDA, and ASCO. Research priorities include: (1) understanding the characteristics of patients who enroll in trials as well as the characteristics of trials that successfully enroll representative older adults; (2) investigation of barriers to provider recruitment of older adults; (3) inclusion of patient advocates in trial design and implementation; and (4) inclusion of geriatric oncologists on review committees and as consultants during the trial design process. Examples of next steps focused on education and culture change are: (1) dissemination and adoption of broadened eligibility criteria recommendations; (2) education and dissemination of evidence supporting the feasibility and efficiency of GAS; (3) provider education focused on communication regarding trial enrollment with older adults; and (4) advocacy-centered education addressing the opportunities for clinical trial engagement for older adults. Finally, recommendations that focused on incentives to overcome barriers include: (1) payment for GAS; (2) increasing accrual credits for recruitment of older adults; (3) inclusion of support for additional patient/caregiver costs (i.e., transportation and lodging) in clinical trial budgets; and (4) inclusion of detailed plans for enrollment of older adults in both industry and NCI-sponsored studies.

Use of Real-World Evidence in Drug Development

The FDA is committed to ongoing efforts to improve the evidence base for treating older adults with cancer. This involves using real-world evidence and patient-reported outcomes (PROs) in the context of regulatory decision-making as it relates to the geriatric oncology population. Real-world data (RWD) is defined as data relating to patient health status and/or delivery of health care routinely collected from a variety of sources, and real-world evidence is defined as clinical evidence regarding the use and potential benefits or risks of a drug derived from the analysis of RWD. The FDA has consistently sought to advance regulatory science that will optimize the decision-making process for the development of cancer therapeutics. From the geriatric oncology perspective, these efforts have great potential to augment our current understanding of oncology drugs in older adults who are traditionally under-represented in clinical trials. The following represent milestones in the FDA’s efforts to improve the framework for RWD collection and analysis:

- In 2008, the FDA launched the Sentinel Initiative in response to the FDA Amendments Act, which called for creation of an active surveillance system for monitoring the safety of approved drugs and products.36
- The FDA Oncology Center of Excellence launched the Information Exchange and Data Transformation (INFORMED) initiative that focuses on building infrastructure in big data analytics.37
- Under the 21st Century Cures Act (2016), the FDA is directed to develop a regulatory framework to evaluate how real-world evidence can potentially be used to support new products and indications and postapproval requirements.38
- FDA’s collaborative efforts with groups like ASCO’s CancerLinQ and Flatiron Health are a prime opportunity to interrogate the data relevant to cancer therapy in older adults.39,40

The FDA recognizes that there is a wealth of RWD that is routinely collected in the course of treatment and management of disease in patients. Although data in the setting of routine clinical practice may not have the same quality controls as data collected within a clinical trial setting, there are circumstances in which RWD may be of sufficient quality to help inform our understanding of approved cancer therapies in older adults. RWD are collected in electronic health records, registries, and claims data. Increasingly, PROs are being captured electronically in the clinical setting, and this can be another pipeline of structured RWD. Data from these various sources could help provide insight into clinical outcomes such as toxicities leading to hospitalizations. This may be of particular importance to a more vulnerable and frail population.

The FDA has encouraged through several guidelines41,42 that sponsors enroll an adequate representation of older adults into their clinical trials; however, in some cases, this may not be achieved. RWD is a potential resource to gather information on patients who are not included in clinical trials, but are treated in clinical practice. As the definition of clinical data derived from electronic health records and other sources expands, more information from older patients in rural and community practices can also be effectively used.

Ongoing collaborations between the FDA and both Flatiron and CancerLinQ have already shown promise. A multicenter analysis using electronic health record data from community clinics in the Flatiron Health Network examined real-world usage patterns of PD-1 inhibitors in metastatic non–small cell lung cancer. The median age of patients at the time of PD-1 inhibitor initiation was 69, with the majority of patients over age 65. Importantly, 27% of patients were age 75 and older.43 This is of particular relevance given an FDA analysis of clinical trial data that showed that whereas 37% of new cases of lung cancer occur in patients 75 and older, they make up only 9% of the clinical trial population.4 In addition to demographic data, RWD can provide additional safety data in the postmarket setting for patient groups not represented in the registration trials.

RWD has potential to inform us on patients traditionally underrepresented in clinical trials. Older adults are a key population of interest in whom there is an increasing need for quality safety data not captured within the current paradigm of clinical trials. To maximize information gained, efforts will need to be made to systematically integrate elements of the GA into routine clinical practice and to capture these data in the electronic health record. The FDA is
committed to this effort through collaboration with both internal and external stakeholders to enhance the capability of this emerging resource. ASCO’s CancerLinQ is rapidly expanding its scope and capability, with a database of over 1 million patients. By recognizing the value of real-world evidence as an important contributing factor for understanding oncology drugs in older adults, we can encourage the medical community to learn more from routine clinical care than we do today.

Patient-Focused Drug Development/PROs
The patient experience is relevant in the evaluation of novel oncology therapeutics for use in all patients but particularly in older adults. The traditional paradigm for drug evaluation has largely been limited to tumor and survival efficacy endpoints balanced against clinician-reported safety data. The FDA has required that the package inserts of approved products included a “Geriatric Use” subsection that provides pertinent information about the drug’s experience in older adults. Unfortunately, the information included in this section can be limited if older adults have been underrepresented in the registration trial(s).

Although tumor and survival data are consistently obtained, GA information is often not captured in registration trials. The GA provides clinicians with information on the heterogeneity of the aging process beyond chronologic age through evaluation of the individual’s functional status, cognitive function, nutritional status, comorbid conditions, psychological state, and social support. A comprehensive GA can inform discussions of patient preference in terms of QOL measures, which can be particularly important in older patients with cancer because a disease-centered approach may neglect key elements such as degree of social support or a patient’s willingness to tolerate effects of therapy, which may lead to loss of independence. Despite efforts to include GAs in clinical trials, they have had limited uptake in trials designed to support FDA registration.

Although formal GAs are not yet typically incorporated, PROs are commonly submitted to the FDA in marketing applications, and some information collected in the PROs contain GA information. For example, PROs commonly include an assessment of health-related QOL domains (e.g., physical, cognitive, emotional, role, and social), as well as key disease- and treatment-related symptoms. The measures are obtained at baseline and periodically throughout the study timeline. The rigor of PRO assessment has been increasing and is providing a rich source of patient experience data that can complement our understanding of a therapy’s effect on older adults with cancer.

Although PRO measures may not specifically address all areas of the GA, functional status is a critical element of most PRO measures and a critical part of the GA. For example, the GA assesses both basic activities of daily living such as bathing, dressing, and feeding, as well as instrumental or advanced activities of daily living, such as driving or shopping for groceries. Similarly, the EORTC, a widely used PRO tool, asks questions such as:

- “Do you have any trouble taking a long or short walk outside of the house?”
- “Do you need to stay in bed or a chair during the day?”
- “Do you need help with eating, dressing, washing yourself, or using the toilet?”

For older adults with cancer, treatment effects on symptoms and functioning may be as important as treatment effects on survival. PRO measures that capture how patients feel and function can be used in the regulatory context to provide patient experience data, support efficacy, and provide complementary descriptive data to inform tolerability. PRO measures evaluating disease symptoms, treatment side effects, physical function, and health-related QOL are commonly incorporated in randomized chemotherapy trials. The FDA incorporates PRO results into their review of new cancer therapies and communicates informative aspects of the PRO data in FDA product labels. The product label is a limited vehicle to present this rich data source, and FDA supports calls to report this information in the published literature in conjunction with the primary tumor response and survival results to inform treatment effects in older patients with cancer.

In recent years, the FDA has made great progress in incorporating the patient voice into the regulatory process. Several recent legislative efforts have highlighted the importance of incorporating the patient more in drug development, including the sixth reauthorization of the Prescription Drug User Fee Act as well as the 21st Century Cures Act. These efforts will result in the FDA holding numerous public workshops and drafting guidance to industry to engage with stakeholders and convey the current thinking on scientifically rigorous patient-focused drug development. The next several years will focus on transitioning from listening to patient experiences in patient-focused drug-development meetings to developing formal advice on systematically collecting patient-centered information in ways that can inform drug development and regulatory decision-making.

There are also multiple commonly used and translated measurement systems that can assess specific symptoms and multi-item scales such as fatigue that may provide more specific and relevant information. These data are an important adjunct to the traditional efficacy and safety data that are currently evaluated and included in drug labels. Many have advocated for more patient experience data to help evaluate new drugs and biologics for older adults. Future workshops planned under the 21st Century Cures Act allow for additional opportunities for geriatric oncology advocates to provide input on PRO tools that may be of most value to older adults. It will be critical for advocates of cancer care in older adults to participate in this process. Together with investigators, advocates, government, industry, and research institutions, we can fill the knowledge gap needed to improve
the care of our rapidly growing population of older adults with cancer.

CONCLUSION

There is a clear imperative to increase the evidence base to inform care for older adults with cancer. Multiple strategies will be needed that engage and harmonize efforts among a diverse group of stakeholders inclusive of patients, advocates, providers, investigators, societies, NIH, industry, regulators, and payers. Results of these efforts will translate to the goal of providing truly personalized care for older adults with cancer.

References


The effects of the aging immune system (immunosenescence) confer immune dysregulation and have both cellular and humoral aspects. We have found depletion in lymphocyte reserve with increasing age, with fewer naive CD4+ and CD8+ T cells and decreased repertoire in regulatory and memory T cells with an overall development of a pro-inflammatory profile.1-3 These changes can lead to increased susceptibility to infections and less robust response to vaccination. Furthermore, immunosenescence may increase the risk for certain cancers, such as lymphomas, because it also affects B-cell function.4 In patients receiving immune-based treatments for melanoma, older adults have demonstrated reduced levels of tumor-infiltrating lymphocytes, which, in turn, confers worse progression- or disease-free survival.5-7 We also know that unique temporal changes in peripheral blood T-cell subset profiles occur in patients with advanced melanoma and non–small cell lung cancer (NSCLC) when they undergo combination or single-agent immunotherapies, which appear to affect both depth and duration of response.8,9 Finally, newer data support a correlation with frailty in older adults and specific T-cell subset “profiles,” which may have implications on how best to further evaluate older adults of differing baseline functional status in terms of the degree of response, tolerability, and overall clinical benefit of immunotherapy within an immunosenescent milieu.10

FRAILTY AND THE ROLE OF GERIATRIC ASSESSMENT IN CANCER TREATMENT DECISION-MAKING

In the context of oncology, a geriatric assessment (GA) is a multidimensional evaluation of the overall fitness of an older adult to tolerate a proposed cancer treatment plan and follow up, thereby aiding cancer providers in their shared treatment decision-making.11,12 A cancer-specific GA often incorporates measures of functional status, cognition, mood, nutrition, medications, social support, and multimorbidity. GA has been used to evaluate the risk for substantial chemotherapy-related toxicity among older adults with cancer.13,14 Before treatment decisions, the International Society of Geriatric Oncology has recommended that the evaluation, including a GA, be part of clinical practice for caring for older adults with lymphoma and other cancers.12,15 To offer a more abbreviated assessment, the G8 screening

From the National Cancer Centre Singapore, Singapore; Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; University of Rochester, Rochester, NY.

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tool was developed to risk-stratify fit versus frail older patients with cancer who could receive standard treatment compared with those who should undergo further evaluation with a full GA to guide tailoring of cancer therapy.\textsuperscript{16,17} To date, no study has evaluated the role of GA and health-related outcomes in older adults receiving immunotherapy, either single-agent or in combination. Many single-institutional and postmarketing analyses in community practice have examined toxicity and related outcomes among older adults with specific cancer types or those in general; however, data remain somewhat conflicting as to whether older adults with increasing age experience more immune-related adverse events (irAEs) than their younger counterparts in terms of their accounting for line of therapy, functional status, cognitive status, and multimorbidity.\textsuperscript{18-24}

**LUNG CANCER**

**Non–small Cell Lung Cancer**

**Overview.** The anti–PD-L1 inhibitors were first evaluated in patients with advanced-stage NSCLC in the second line or beyond compared with docetaxel chemotherapy.\textsuperscript{25-28} These studies collectively demonstrated an improvement in objective response rate (ORR) of 15% to 20% and overall survival (OS) by approximately 3 to 4 months compared with docetaxel. In the first-line setting in preselected patients with advanced NSCLC with at least 50% PD-L1 expression, ORR and OS were improved compared with results seen with platinum-based doublet chemotherapy.\textsuperscript{29} **Stage III disease.** RTOG 3505 (NCT02768558) was evaluating cisplatin/etoposide-based concurrent chemoradiation therapy, followed by nivolumab, versus placebo maintenance therapy, but this trial was closed early because of results of the PACIFIC trial. That trial evaluated the added benefit of durvalumab versus placebo after platinum-based concurrent chemoradiation (any chemotherapy regimen). It demonstrated significant progression-free survival (PFS) favoring durvalumab compared with placebo (median, 16.8 vs. 5.6 months, respectively); it also almost doubled the time to metastatic recurrence or death compared with placebo (23.2 vs. 14.6 months, respectively). Approximately 4.4% of the patients in the treatment group developed grade 3 to 4 pneumonia, with durvalumab-related or radiation-related pneumonitis leading to durvalumab discontinuation most frequently (4%-6%). However, the median age for each group was younger than age 70 (Table 1). The PFS benefit still appeared significant irrespective of age, but the confidence interval started to cross 1.0 for patients age 65 or older compared with those younger than age 65. Other studies are evaluating the combination of anti–PD-1 inhibitors, such as nivolumab, concurrently with chemotherapy and radiation upfront for stage III NSCLC (e.g., the NICOLAS study, NCT02434081); neoadjuvant chemoradiation plus pembrolizumab followed by surgery for resectable disease followed by maintenance pembrolizumab (NCT02987998); and studies evaluating this class of agents in combination with stereotactic body radiation therapy for both oligometastatic and localized NSCLC.

**Anti–PD-1 and anti–PD-L1 therapy: second-line and beyond.** Despite relative under-representation of older adults, pooled analyses have demonstrated that older adults are still likely to benefit in terms of OS when receiving immunotherapy for advanced solid tumors, including NSCLC.\textsuperscript{20,22,30-33} For NSCLC, when age 65 or older was used as a cutoff, there was a relative risk reduction in mortality of 34% favoring immunotherapy over chemotherapy.\textsuperscript{32} Despite these limitations, age-based subgroup analyses have been performed in some NSCLC trials. For example, in CheckMate 017 and 057, which led to nivolumab’s approval in the second line and beyond for advanced NSCLC, although only 7% to 10% of the total patients enrolled were age 75 or older, subset analysis demonstrated a trend in limited clinical benefit or worse overall mortality.\textsuperscript{25,26} An expansion trial of nivolumab in this setting was evaluated to capture more patients age 70 or older and/or those with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (CheckMate 153).\textsuperscript{22} Of the approximately 1,300 patients enrolled, 40% were age 70 or older and 9% had ECOG PS of 2. Of the patients with a PS of 2, half were age 70 or older. However, many of these patients were heavily pretreated; more than half had received two or more lines of therapy. In a comparison of younger (< age 70) versus older (≥ age 70) patients, there were no differences in treatment discontinuation rates (79% vs. 78%), toxicity of any grade (60% vs. 62%); grade 3 to 4 toxicity (11% vs. 13%), or median OS (9.4 vs. 10.3 months). Tumor PD-L1 expression was not broken down further by age.

**Anti–PD-1 therapy first-line: alone and in combination with chemotherapy.** KEYNOTE 024 evaluated first-line pembrolizumab compared with platinum-based chemotherapy as frontline therapy for patients with advanced NSCLC whose tumors had at least 50% PD-L1 expression.\textsuperscript{29} The median age

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**PRACTICAL APPLICATIONS** & \\
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- Older adults remain under-represented in cancer clinical trials, including those involving immunotherapies. & \\
- Older adults with good performance status appear to benefit similarly to single-agent checkpoint inhibitor therapy (i.e., PD-1 or PD-L1) as their younger counterparts. & \\
- Overall toxicity appears similar both across landmark trials and in single-institutional studies, but hospitalizations and influence of poor functional status and multimorbidity in the real world remain. & \\
- The role of a geriatric assessment for older adults receiving immunotherapies remains unclear but may be useful to gauge fitness for more intense therapies, such as combined immunotherapy, chemoimmunotherapy, or chemotherapy/radiation plus immunotherapy strategies & \\
- More research is needed to evaluate the correlation between markers of immunosenescence among older adults receiving immunotherapy and the effect of these relationships on biological, clinical, functional, and patient-reported outcomes. & \\
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<tr>
<th>Trial</th>
<th>Setting</th>
<th>Treatment</th>
<th>Age Data*</th>
<th>ECOG/WHO PS</th>
<th>Primary Outcome(s)</th>
<th>Age- or PS-Specific Subgroup Analyses: HR (95% CI)**</th>
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<tr>
<td><strong>NSCLC stage III</strong></td>
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<td>PACIFIC</td>
<td>Stage IIA-B, first-line</td>
<td>CRT with any platinum-based chemotherapy followed by durvalumab or placebo for 1 year</td>
<td>Median: age 64; Range: age 23–90; Age ≥ 65: 322 (45%)</td>
<td>0; 49%; 1: 51%</td>
<td>PFS</td>
<td>For PFS benefit with durvalumab after CRT: &lt; age 65: 0.43 (0.47–0.73); ≥ age 65: 0.74 (0.54–1.01)</td>
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<td><strong>NSCLC advanced stage, second-line, and beyond</strong></td>
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<td>CheckMate 017</td>
<td>Stage IIIB/IV</td>
<td>Nivolumab vs. docetaxel</td>
<td>Median: age 63; Range: age 39–85; Age 65–74: 91 (33%); Age ≥ 75: 29 (11%)</td>
<td>0; 24%; 1: 76%</td>
<td>OS, PFS</td>
<td>For OS benefit with nivolumab: &lt; age 65: 0.52 (0.35–0.75); age 65–74: 0.56 (0.34–0.91); ≥ age 75: 1.85 (0.76–4.51)</td>
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<tr>
<td>CheckMate 057</td>
<td>Stage IIIB/IV</td>
<td>Nivolumab vs. docetaxel</td>
<td>Median: age 62; Range: age 21–85; Age 65–74: 200 (34%); Age ≥ 75: 43 (7%)</td>
<td>0; 31%; 1: 69%</td>
<td>OS, PFS</td>
<td>For OS benefit with nivolumab: &lt; age 65: 0.81 (0.62–1.04); age 65–74: 0.53 (0.45–0.89); ≥ age 75: 0.90 (0.43–1.87)</td>
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<td>KEYNOTE 010</td>
<td>Stage IIIB/IV</td>
<td>Pembrolizumab (2 doses) vs. docetaxel</td>
<td>Median: age 63; Range: age 56–69; Age ≥ 65: 429 (41.5%)</td>
<td>0; 34%; 1: 66%; 2–3: &lt; 1%</td>
<td>OS, PFS</td>
<td>For OS benefit with pembrolizumab: &lt; age 65: 0.63 (0.50–0.79); ≥ age 65: 0.76 (0.57–1.02)</td>
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<tr>
<td>OAK</td>
<td>Stage IIIB/IV</td>
<td>Atezolizumab vs. docetaxel</td>
<td>Median: age 64; Range: age 33–85; Age ≥ 65: 397 (47%)</td>
<td>0; 37%; 1: 63%</td>
<td>OS</td>
<td>For OS benefit with atezolizumab: &lt; age 65: 0.80 (0.64–1.00); ≥ age 65: 0.66 (0.52–0.83); PS 0: 0.78 (0.58–1.04), PS 1: 0.68 (0.56–0.84)</td>
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<td>Trial</td>
<td>Setting</td>
<td>Treatment</td>
<td>Age Data*</td>
<td>ECOG/WHO PS</td>
<td>Primary Outcome(s)</td>
<td>Age - or PS-Specific Subgroup Analyses: HR (95% CI)**</td>
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<td><strong>NSCLC advanced stage, first-line</strong></td>
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<td>KEYNOTE 024</td>
<td>Stage IV</td>
<td>Pembrolizumab vs. platinum-based chemotherapy</td>
<td>Median: age 64.5; age 66 (each group)</td>
<td>0: 35%; 1: 65%</td>
<td>OS</td>
<td>For OS benefit with pembrolizumab: &lt; age 65: 0.61 (0.40–0.92); ≥ age 65: 0.45 (0.29–0.70)</td>
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<td>First line, PD-L1 ≥ 50%</td>
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<td>Range: age 33–90</td>
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<td>Age ≥ 65: 164 (54%)</td>
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<td>CheckMate 026</td>
<td>Recurrent/stage IV</td>
<td>Nivolumab vs. platinum-based chemotherapy</td>
<td>Median: age 65</td>
<td>0: 33%; 1: 66%; 2–3: 1%</td>
<td>OS</td>
<td>For OS benefit with nivolumab: &lt; age 65: 1.13 (0.83–1.54); ≥ age 65: 1.04 (0.77–1.41); PS 0: 1.11 (0.74–1.66); PS ≥ 1: 1.02 (0.79–1.32)</td>
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<td>Age ≥ 65: 260 (48%)</td>
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<td>Age ≥ 75: 62 (11%)</td>
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<td>KEYNOTE 021</td>
<td>Stage IIIB/IV, nonsquamous cell</td>
<td>Pembrolizumab + carboplatin/pemetrexed vs. chemotherapy alone</td>
<td>Median: age 63</td>
<td>0: 44%; 1: 56%</td>
<td>ORR</td>
<td>&lt; age 65 vs. ≥ age 65 for ORR planned but not yet reported</td>
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<td>Range: age 54–70</td>
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<td>Govindan et al</td>
<td>Recurrent/stage IV</td>
<td>Ipilimumab + carboplatin/paclitaxel vs. placebo + chemotherapy</td>
<td>Median: age 64</td>
<td>0: 34.5%; 1: 64.8%; 2–3: 0.7%</td>
<td>PFS</td>
<td>For PFS benefit with addition of ipilimumab: &lt; age 65: 0.82 (0.64–1.04); age 65–74: 1.06 (0.81–1.37); ≥ age 75: 0.85 (0.51–1.43); PS 0: 0.99 (0.73–1.33); PS 1: 0.86 (0.70–1.05)</td>
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<td>Age &lt; 65: 280 (37%)</td>
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<td>Age 65–74: 298 (40%)</td>
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<td>Age ≥ 75: 71 (9%)</td>
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<td><strong>Small cell lung cancer</strong></td>
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<td>CheckMate 032</td>
<td>Progressive disease after platinum-based chemotherapy, second line or beyond</td>
<td>Nivolumab vs. nivolumab + ipilimumab (2 differing doses: 1 mg/kg + 3 mg/kg vs. 3 mg/kg + 1 mg/kg)</td>
<td>Median: age 63; age 66; age 61</td>
<td>All were 0–1; breakdown not available</td>
<td>ORR</td>
<td>None reported</td>
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<td></td>
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<td>Age ≥ 75: 9 patients; 7 patients; 0 patients (8% of total study population)</td>
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<td>Range: age 46–71</td>
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<table>
<thead>
<tr>
<th>Trial</th>
<th>Setting</th>
<th>Treatment</th>
<th>Age Data*</th>
<th>ECOG/WHO PS</th>
<th>Primary Outcome(s)</th>
<th>Age- or PS-Specific Subgroup Analyses: HR (95% CI)**</th>
</tr>
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<tbody>
<tr>
<td><strong>Metastatic urothelial carcinoma</strong></td>
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<tr>
<td>KEYNOTE 045</td>
<td>Advanced UC, progressed after platinum-based chemotherapy</td>
<td>Pembrolizumab vs. investigators' choice (docetaxel or paclitaxel or vinflunine)</td>
<td>Median: age 67</td>
<td>0: 44.1%; 1: 53.0%; 2: 0.7%</td>
<td>OS, PFS</td>
<td>For OS ≥ age 65: 0.76 (0.56–1.02)</td>
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<td>Range: age 29–88</td>
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<tr>
<td>CheckMate 275</td>
<td>Advanced UC, progressed after platinum-based chemotherapy</td>
<td>Phase II single arm with nivolumab</td>
<td>Median: age 66</td>
<td>0: 54%; ≥ 1: 46%</td>
<td>ORR</td>
<td>None reported</td>
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<td>Range: age 38–90</td>
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<tr>
<td>KEYNOTE 052</td>
<td>Locally advanced, unresectable or MUC cisplatin-ineligible patients</td>
<td>Single arm phase II with pembrolizumab</td>
<td>Median: age 74</td>
<td>0: 22%; 1: 36%; 2: 42%; 3: &lt; 1%</td>
<td>ORR</td>
<td>ORR for patients who responded for ≥ 4 months were stratified for age: ≥ age 65: 26%, ECOG 2: 27%</td>
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<td>Range: age 38–90</td>
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<td></td>
<td>Age &gt; 65: &gt; 80%</td>
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<tr>
<td>IMVIGOR 210</td>
<td>Locally advanced, unresectable or MUC cisplatin-ineligible patients</td>
<td>Single-arm phase II with atezolizumab</td>
<td>Median: age 73</td>
<td>2: 20.2%</td>
<td>ORR</td>
<td>ORR ≥ age 80: 28%</td>
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<td></td>
<td>Range: age 51–92</td>
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</table>

*Values are expressed as median age, age range, and/or number (percentage) of patients.

**Values are hazard ratios and 95% CIs except for last two studies, which are objective response rates.

Abbreviations: CRT, chemoradiation therapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; MUC, metastatic urothelial carcinoma; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; UC, urothelial carcinoma; WHO, World Health Organization.
was 64.5 to 66 (range, age 33–90). The ORR, PFS, and OS were statistically significantly improved, favoring upfront pembrolizumab, in this PD-L1–high NSCLC population; in age-based subgroup analysis (< age 65 vs. ≥ age 65), this superiority was maintained (hazard ratio for risk for death or progression was 0.61 vs. 0.45, respectively; Table 1). Seventy-three percent and 26% of patients experienced any grade and grade 3 to 5 toxicities, respectively. Only 7% of these toxic events led to treatment discontinuation; these rates were statistically lower than those seen in the chemotherapy group (90%, 53%, and 11%, respectively). For the irAEs, 29% were any grade and 10% were grade 3 to 4; most were dermatologic (4%). CheckMate 026 evaluated nivolumab compared with platinum-based combination chemotherapy as frontline therapy for patients with advanced NSCLC. Median age of patients enrolled was 64 (range, age 29–89); 11% were age 75 years or older. This study did not a priori exclude patients with tumors exceeding a prespecified level of PD-L1 expression and was restricted to those with an ECOG PS of 0–1. Age-based subgroup analyses did not show any difference in ORR, PFS, or OS advantage in this unselected NSCLC patient population. However, for the primary OS analysis, patients were stratified by PD-L1 level by using a cutoff of 5%, which failed to meet the primary aim. Only in subgroup analysis looking at high tumor mutation burden and PD-L1 levels of 50% or greater did the data support a trend toward improved survival outcomes with nivolumab. Toxicity for upfront nivolumab therapy was similar to that seen for pembrolizumab in the KEYNOTE 024 trial, with 71% experiencing any grade toxicity and 18% experiencing grade 3 to 4 events. Only 10% of events led to treatment discontinuation, which was improved overall compared with chemotherapy. Interestingly, with advancing age, there was a trend toward decreasing tumor mutation burden seen irrespective of treatment (approximately 50% for patients younger than age 65, 37% for patients age 65–74, and 12%–15% for patients age 75 or older). Analogously, of patients with tumors with at least 5% PD-L1 expression, just over half (53%) were younger than age 65, 34% were age 65 to 74, and 12% were age 75 or older.

The recent phase I CheckMate 012 trial evaluated lower-intensity ipilimumab plus nivolumab as first-line therapy for advanced NSCLC independent of PD-L1 expression. The median age of patients enrolled was 62 to 68, but the study was limited to patients with an ECOG PS of 0–1. Almost three quarters of patients experienced any grade toxicity, with almost a third incurring grade 3 to 4 events. Severe irAEs or events leading to treatment discontinuation occurred in no more than 5% of patients regardless of ipilimumab schedule. The median duration of response was about 9 months and the ORR was 38% to 48% depending on the regimen; more favorable outcomes trended commensurately with tumor levels of PD-L1 expression. Compared with historical controls from the CheckMate 026 nivolumab monotherapy first-line trial, ORR and disease control rates were relatively improved, particularly among patients who had tumors with higher levels of PD-L1 expression.

Two recent studies explored first-line chemoinmunotherapy (Table 1). First, KEYNOTE 021 evaluated pembrolizumab in combination with carboplatin plus pemetrexed with pemetrexed maintenance versus chemotherapy alone, irrespective of tumor PD-L1 status, among patients with advanced adenocarcinoma of the lung. With an impressive ORR (all partial responses [PRs]) of 55% favoring the combination treatment, there was still a trend toward a higher frequency of grade 3 to 5 adverse events (AEs) in the combination group (39% vs. 26%, but only 8% of events leading to treatment discontinuation); the rate of any grade irAE was 19% and the rate of grade 3 to 4 irAEs was 2% in an ECOG PS 0–1 patient population with a median age of 62.5 to 63.2 (range, age 54–70). Median PFS appears superior for the combination group (19 vs. 9 months), but OS benefit remains unclear yet encouraging. Another trial evaluated frontline ipilimumab versus placebo combined with carboplatin plus gemcitabine for advanced squamous cell carcinoma of the lung. Patients enrolled were generally younger (median age, 64; range, age 28–85), with only 10% age 75 or older; almost all had an ECOG PS of 0–1. Unfortunately, the combination did not significantly improve ORR, OS, or PFS; moreover, toxicities were much higher than those seen with chemotherapy plus placebo: 51%, 33%, and 28% versus 35%, 10%, and 7%, respectively, for any grade toxicity, grade 3 to 4 toxicity, or discontinuation due to toxicity. Seven treatment-related deaths occurred in the treatment group vs. one in the placebo group. Of the irAEs, 27% were related to diarrhea.

Small Cell Lung Cancer
Growing data support the clinical benefit of immunotherapy in the second line or beyond for patients with extensive-stage small cell lung cancer, particularly nivolumab alone or in combination with ipilimumab. However, how best to sequence immunotherapy in platinum-resistant or refractory disease while balancing the potential toxicities of combination therapy in particular patients remains unanswered questions. Furthermore, the incorporation of other predictive biomarkers that may be more germane in the small cell arena, such as tumor mutation burden (given relatively lower PD-L1 expression, particularly in small cell cancer), may help further stratify monotherapy and combination treatment decision-making.

METASTATIC UROTHELIAL CARCINOMA Overview
Urothelial cancer is the fourth most common cancer in males and 11th most common cancer in females in the Western population. After prostate cancer, it is the second most common urinary tract malignancy. Similar to NSCLC, it is usually diagnosed in older adults, with a median age of 70 at diagnosis. Despite the prevalence of bladder cancer, mortality rates have remained unchanged in the past 20 years. The 5-year OS rate stands at 70% for localized bladder cancer. However, survival rates strikingly decline for locally advanced or metastatic disease, with the median OS being approximately 15 months. Urothelial carcinoma can be categorized into...
three groups: nonmuscle invasive, muscle-invasive, or metastatic. Muscle-invasive disease makes up 20% to 30% of cases and treatment involves cystectomy with neoadjuvant or adjuvant chemotherapy.42 Cisplatin-based combination chemotherapy has been the standard of care for metastatic urothelial carcinoma (MUC) for the past 20 years, with dismal survival rates.43 The lack of efficacious treatment options for patients with advanced urothelial carcinomas underscores the need for novel treatment strategies. In recent times, immunotherapy has made the headlines for its potential to change treatment paradigms in many cancers, including bladder cancer.44 Intravesical bacillus Calmette-Guerin was the first U.S. Food and Drug Administration–approved immunotherapy for use in nonmuscle invasive bladder cancer. Most recently, immune checkpoint inhibitors have become the face of immunotherapy in the treatment of MUC.

**Cisplatin-eligible MUC.** Immune checkpoint inhibitors are a particularly attractive treatment option for bladder cancers because bladder cancers are highly antigenic, with the third highest rates of somatic mutations after melanoma and NSCLC.44 Atezolizumab, a monoclonal IgG1 antibody that binds PD-L1, was the first anti–PD-L1 antibody that was U.S. Food and Drug Administration approved for use in metastatic bladder cancer after failure of chemotherapy.45 Pembrolizumab, a PD-1 inhibitor, was first studied in the phase IB KEYNOTE 012 trial, which included patients with metastatic and locally advanced urothelial cancers. After a median follow-up of 13 months, eight of 33 patients (28%) responded to treatment. Of these, three had complete responses (CRs).46

This trial was followed by the phase III KEYNOTE 045 study, which was an international randomized controlled trial. A total of 542 patients with advanced urothelial carcinoma that progressed after platinum-based chemotherapy were randomly assigned to pembrolizumab or investigator’s choice of chemotherapy (paclitaxel, docetaxel, or vinflunine). The median age of patients in the pembrolizumab group was 67 (range, age 29–88). The coprimary endpoints of the trial were OS and PFS in the overall cohort and the cohort of patients with metastatic and locally advanced urothelial cancers. After a median follow-up of 13 months, eight of 33 patients (28%) responded to treatment. Of these, three had complete responses (CRs).46

Despite the research, we still do not know which patient with MUC will benefit from immunotherapy and who will do better with chemotherapy. A predictive biomarker will not only help to personalize treatment but also spare patients who will not benefit from the drug because of AEs and the financial toxicity from these expensive drugs. PD-L1 has been used as a surrogate marker for efficacy in cancers such as NSCLC. A meta-analysis on the role of PD-L1 status showed higher response rates in patients with higher PD-L1 expression.47 However the value of PD-L1 as a biomarker in urothelial cancers is limited at present. In the phase ii IMvigor210 trial studying the role of atezolizumab in cisplatin-ineligible patients, patients with tumors with higher PD-L1 expression on immune cells demonstrated a higher response rate compared with lower PD-L1 expression (ORR, 26% vs. 10%, respectively).48

However, this was contrary to the findings of the CheckMate 275 and KEYNOTE 045 trials. In the CheckMate 275 trial, patients with metastatic bladder cancer whose disease progressed while receiving platinum-based chemotherapy were given nivolumab at 3 mg/kg. Nivolumab was efficacious across all PD-L1 subgroups, with an ORR of 19.6% in the overall population and 16% in the low–PD-L1 expression subgroup.49 In the KEYNOTE 045 trial, pembrolizumab showed an OS benefit over chemotherapy regardless of PD-L1 expression.50 The conflicting results of PD-L1 status in the different studies may be related to various factors. First, different methods were used to determine PD-L1 expression, for example, testing methods, assays used, and how expression was defined (tumor cells, tumor-infiltrating immune cells, or a combination thereof). Second, in many
instances stored archival tumor tissues were used instead of new biopsy specimens, which is not ideal given that PD-L1 expression may change commensurately with the disease stages and prior lines of therapies.

Although checkpoint inhibitors are better tolerated than early immunotherapeutic agents, such as interleukin-2, they do have AEs. Some common toxicities include fatigue, dermatologic manifestations (e.g., rash and pruritus), diarrhea independent of colitis, and endocrinopathies such as hypophysitis and thyroiditis. Less common but potentially life-threatening toxicities that have been encountered include pneumonitis, colitis, and pancreatitis. Although most toxicities resolve with drug withdrawal and prompt initiation of systemic corticosteroids, endocrinopathies tend to be irreversible, require ongoing monitoring, and lead to lifelong steroid and/or hormone replacement.

LYMPHOMAS

Overview

Compared with other cancers, non-Hodgkin lymphoma (NHL) is common, representing 4.3% of all new cancer causes in the U.S. National Cancer Institute Surveillance, Epidemiology, and End Results (NCI SEER) program reveals that the median age at diagnosis of NHL is 67, with 24.9% of new cases being diagnosed in patients age 65 to 74, 21.3% of those age 75 to 84, and 9.4% of those older than age 84. Increasing age is associated with poorer OS in patients with NHL. In fact, age is among the prognostic factors in the International Prognostic Index scoring for histologically aggressive lymphoma and the Follicular Lymphoma International Prognostic Index scoring for follicular lymphoma (FL).

There is a lack of consensus about the age at which a patient with NHL is considered “older” or “elderly,” with a conventional definition of older than age 65, although many argue it should be older than age 75 because of the more substantial physiologic and pharmacologic changes that occur around that time.

Immunotherapy for Lymphomas: Overview

Although cases in older adults represent most of the cancers diagnosed and deaths by age group, they are underrepresented in clinical trials. Aging is also associated with a decrease in the effectiveness of the immune system and in alterations to it. Few specific trials have been carried out for immunotherapy in elderly people, with most patients considered to be fit. Tolerance among older adults seems to be similar to that of younger adults, but efficacy seems to differ according to the type of cancer; some show no difference and others less efficacy among older subgroups. However, the numbers in older subgroups are relatively small and more investigation is needed, with specific clinical trials for elderly patients with cancer.

Lymphomas have previously demonstrated substantial responsiveness to immunologic manipulations. B-cell lymphomas demonstrate an interplay between tumor and the host immune system that appears to directly affect lymphoma growth. Other lymphomas, such as FL, contain many tumor-infiltrating lymphocytes in the tumor microenvironment that are potential candidates for checkpoint blockade to elicit local immune activation against malignant B cells.

Following the successful use of immune checkpoint blockade therapy in advanced solid tumors, these agents have become a promising modality in the treatment of relapsed lymphomas. To date, the PD-1 and PD-L1 pathway has emerged as a key target of checkpoint inhibitor therapy, demonstrating unprecedented activity, particularly in heavily pretreated relapsed/refractory HL and some forms of NHL. Studies of checkpoint inhibitors in lymphomas are reviewed below by agent: the anti–PD-1 antibodies nivolumab and pembrolizumab, the anti–delta-like-1/PD-1 antibody pidilizumab, and the anti–PD-L1 antibody atezolizumab. Landmark clinical trials of these agents in older patients with lymphomas are summarized below (Table 2).

Specific Lymphomas: Hodgkin Lymphoma

The phase I study of nivolumab in Hodgkin lymphoma (HL) showed an 87% ORR; 17% of patients reached CR and 70% achieved PR. Twenty-three patients were enrolled, with a median age of 35 (range, age 20–54). The phase II CheckMate 205 study of nivolumab in patients with relapsed/refractory classic HL after failed autologous stem cell transplantation and brentuximab vedotin demonstrated an ORR of 66%, with seven patients achieving CR (9%) and 46 patients reaching PR (58%). This study enrolled slightly more patients (80 patients), with a median age of 39 (range, age 18–72); however, only three patients (4%) were age 65 or older.

A subgroup analysis, categorized by age, was performed on data reported in patients with classic HL receiving nivolumab at 3 mg/kg intravenously every 2 weeks in studies CA209-205 (phase II) and CA209-039 (phase I). In the integrated population of both studies, the efficacy of nivolumab was evaluated in 95 patients and safety was evaluated in 266 patients with classic HL. At baseline, the median age was 37 (range, age 18–72), with only 3.2% of patients age 65 or older. The ORRs were 66.3% (95% CI, 55.7–75.8) in those younger than age 65 and 66.7% (95% CI, 9.4–99.2) in those age 65 or older. This analysis showed frequencies of grade 3 to 4 AEs, all-causality and drug-related, were greater among patients age 65 or older than among those younger than age 65, as follows: (1) younger than age 65: all-causality grade 3 to 4 AEs, 37.5%; drug-related grade 3 to 4 AEs, 20.8% and (2) age 65 or older: all-causality grade 3 to 4 AEs, 42.9%; drug-related grade 3 to 4 AEs, 28.6%. Any differences noted are of limited interpretability because of low sample sizes and event rates and probably do not alter the overall safety profile of nivolumab in these subgroups. However, further study is warranted. In a real-life-experience study of nivolumab in 82 patients with relapsed or refractory HL, the median age was 30 (range, age 18–75). Patients older than age 65 were included, but safety and efficacy have not differed.

New trials are exploring nivolumab in combination with other therapies. According to the interim results of a phase I/II trial of brentuximab vedotin plus nivolumab in 62 patients with relapsed or refractory HL, the median age was 36 (range, age 18–69). The CR rate among all treated patients
### TABLE 2. Summary of Landmark Immunotherapy Trials in Lymphomas With Focus on Older Adult Representation

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Antibody, Dose</th>
<th>Phase; No. of Patients</th>
<th>ORR, %; CR, %</th>
<th>PFS (%); OS: Duration of Response</th>
<th>All-Grade AEs, Grade 3–4 AEs</th>
<th>Median Age (Range), Years</th>
<th>Older Adults (≥ Age 65), N (%)</th>
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<tbody>
<tr>
<td><strong>HL</strong></td>
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<tr>
<td>R/R cHL</td>
<td>Nivolumab, 3 mg/kg every 2 weeks</td>
<td>Phase I; 23</td>
<td>87, 17</td>
<td>PFS: 86 at 24 weeks; OS: 91 at 1 year; 83 at 1.5 y</td>
<td>78, 22</td>
<td>35 (20–54)</td>
<td>0 (0)</td>
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<td>R/R cHL that progressed after BV</td>
<td>Pembrolizumab, 10 mg/kg every 2 weeks</td>
<td>Phase IB; 32</td>
<td>65, 16</td>
<td>PFS: 46 at 52 weeks</td>
<td>97, 16</td>
<td>32 (20–67)</td>
<td>1 (3)</td>
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<tr>
<td>R/R cHL that failed to respond to AHSCT and BV</td>
<td>Pembrolizumab, 3 mg/kg every 2 weeks</td>
<td>Phase II; 80</td>
<td>66.3, 9 (68, 13 according to ICML 2017 update)</td>
<td>At 6 months: PFS: 76.9; OS: 98.7; at 12 months, median PFS: 10.0 months</td>
<td>99, 41</td>
<td>39 (18–72)</td>
<td>3 (4)</td>
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<td>R/R cHL, progressed after ASCT and/or BV</td>
<td>Pembrolizumab, 200 mg once every 3 weeks, (median no. of treatment cycles: 13)</td>
<td>Phase II; 210</td>
<td>69, 22.4</td>
<td>At 6 months: PFS: 72.4; OS: 99.5</td>
<td>All: 63 irAEs: 28.6; infusion-related reactions: 6.4</td>
<td>All patients: 35 (18–76)</td>
<td>All patients: 18 (8.6)</td>
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<tr>
<td>R/R NHL and MM</td>
<td>Nivolumab, 1–3 mg/kg every 2 weeks</td>
<td>Phase IB; FL: 10, DLBCL: 11, other B-NHL: 10, T-cell NHL: 23, MM: 27</td>
<td>FL: 40, 10; DLBCL: 36, 18; other B-NHL: 0, 0; T-cell NHL: 17, 0; MM: 4, 4</td>
<td>Duration of response: 6.0–81.6 weeks</td>
<td>All: 63; (for B-cell NHL: 71, 26)</td>
<td>B-cell lymphoma 65 (23–74)</td>
<td>T-cell lymphoma 61 (30–81)</td>
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<tr>
<td>R/R PMBCL</td>
<td>Pembrolizumab, 10 mg/kg every 2 weeks or 200 mg every 3 weeks for up to 2 years</td>
<td>Phase IB; 18</td>
<td>41, 11.8</td>
<td>With median follow-up of 11.3 months, median duration of response and OS were not reached; in 2 of the 7 patients who responded, duration of response was 20.5+ and 22.4+ months</td>
<td>61, 11.8</td>
<td>30 (22–62)</td>
<td>0 (0)</td>
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<tr>
<td>R/R CLL with RT and relapsed CLL</td>
<td>Pembrolizumab, 200 mg every 3 weeks for up to 2 years</td>
<td>Phase II; 25 RT: 9, relapse CLL: 16</td>
<td>RT: 44, 11; relapsed CLL: 0, 0</td>
<td>Median OS: 10.7 months for R/R CLL with RT after a median follow-up time of 11 months, not reached among patients with prior ibrutinib therapy</td>
<td>100, 60</td>
<td>Total: 69 (46–81)</td>
<td>RT*: 4 (44)</td>
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Continued
### TABLE 2. Summary of Landmark Immunotherapy Trials in Lymphomas With Focus on Older Adult Representation (Cont'd)

<table>
<thead>
<tr>
<th>Lymphoma</th>
<th>Antibody, Dose</th>
<th>Phase; No. of Patients</th>
<th>ORR, %; CR, %</th>
<th>PFS (%); OS: Duration of Response</th>
<th>All-Grade AEs, Grade 3–4 AEs</th>
<th>Median Age (Range), Years</th>
<th>Older Adults (≥ Age 65), N (%)</th>
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<tbody>
<tr>
<td>R/R PCNSL and PTCL</td>
<td>Nivolumab, 3 mg/kg intravenously every 2 weeks (in 1 patient with rituximab-refractory PCNSL, rituximab was continued for 3 doses after initiation of nivolumab treatment)</td>
<td>R/R PCNSL: 4, PTCL with CNS relapse: 1</td>
<td>100, 80</td>
<td>3 patients remained free of progression at 13+ to 17+ months</td>
<td>60, 20</td>
<td>64 (54–85)</td>
<td>3 (60)</td>
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* Nivolumab therapy after radiotherapy.
** Age ≥ 70.

Abbreviations: AE, adverse event; AHSCT, autologous hematopoietic stem cell transplantation; ASCT, autologous stem cell transplant; BV, brentuximab vedotin; cHL, classic-type Hodgkin lymphoma; CLL, chronic lymphocytic leukemia; CNS, central nervous system; CR, complete response; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; irAE, immune-related adverse event; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; ORR, objective response rate; OS, overall survival; PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; PMBCL, primary mediastinal B-cell lymphoma; PTCL, peripheral T-cell lymphoma; R/R, relapsed/refractory; RT, Richter transformation.
was 61%, with an ORR of 82%. Five patients (8%) were treated with systemic steroids for irAEs. The combination of brentuximab vedotin and nivolumab was an active and well-tolerated first salvage regimen that potentially provided patients with relapsed or refractory HL an alternative to traditional combination chemotherapy. Although it is an attractive regimen for elderly patients with relapsed or refractory HL, for whom chemotherapy approaches are usually not feasible, we still do not have robust data on safety and efficacy of this “chemotherapy-free” combination in older adults with HL.

Pembrolizumab has also shown substantial efficacy in patients with relapsed or refractory HL. Updated results from KEYNOTE 013 (31 patients), with a median patient age of 32 (range, age 20–67) and a median follow-up of 24.9 months, showed an ORR of 58% (18 of 31), a CR rate of 19% (6 of 31), and a PR rate of 12% (12 of 31); the median duration of response was not yet been reached.69 The phase II KEYNOTE 087 study (205 patients) evaluated pembrolizumab in three cohorts of patients with classic HL defined by history of exposure to brentuximab vedotin and autologous stem cell transplantation. Of the entire cohort, only 8.6% (18 patients) were age 65 or older. Pooled preliminary data from the three cohorts showed an ORR of 65.4% to 68.3%, a CR rate of 21.7% to 29%, and reduced tumor burden in 93.7%. This preliminary study shows substantial clinical activity of pembrolizumab across different lines of prior treatment and age ranges.70

Clinical development of anti–PD-1 therapy in classic HL continues, with a planned phase III trial of nivolumab monotherapy for classic HL, a study of it in combination with brentuximab vedotin versus brentuximab vedotin alone (CheckMate 812), a phase III trial comparing pembrolizumab head-to-head with brentuximab vedotin (KEYNOTE 204), and studies evaluating treatment with PD-1 blockade earlier in the natural history of classic HL. Both trials allow the recruitment of older adults, so reporting of specific subgroup analyses of these trials is eagerly awaited.

Non-Hodgkin Lymphoma: Anti–PD-1 Therapy

Pidilizumab was evaluated in a phase I study of 66 patients with diffuse large B-cell lymphoma (DLBCL) after autologous stem cell transplantation. The median age at enrollment was 57 (range, age 19–80).71 This study had an ORR of 51%, and 70% of patients did not have progressive disease at 16 months. Although older adults were enrolled, no mention was done regarding differences in safety or efficacy. A study of pidilizumab plus rituximab in 32 patients with relapsed FL demonstrated an ORR of 66% (19 of 29 evaluable patients) and 15 CRs were noted (52%). The median age at enrollment was 61 (range, age 35–79), and no differences among age subgroups were mentioned.72 The clinical development of pidilizumab has been delayed by doubts about its target because it does not bind PD-1; recent evidence suggests that the delta-like 1 protein is the primary binding target, whereas PD-1 is secondary and restricted to nonglycosylated and hypoglycosylated forms of this molecule.73

Among a study across several lymphoma types, nivolumab monotherapy in FL showed a 40% ORR (4 of 10), with one CR (10%), three PRs (30%), and six with stable disease (60%), with median PFS not reached.74 In the B-cell lymphoma cohort of this study, the median age at enrollment was 65 (range, age 23–74), with no differences among young and older patients reported. The KEYNOTE 013 study included 19 patients with primary mediastinal B-cell lymphoma (PMBCL), with a median age of 30.5 (range, age 22–62); pembrolizumab showed a response rate of 41%, with two patients achieving CR and five achieving PR.75 A phase II study (KEYNOTE 170) is planned on the basis of these results, with no age limit in eligibility criteria.

In T-cell NHL, pembrolizumab has also shown clinical activity for relapsed/refractory advanced mycosis fungoides and Sézary syndrome, with an ORR of 38%, with one CR and eight PRs.76 The aforementioned study of nivolumab included 23 patients with T-cell NHL in which there were four PRs: two of 13 patients (15%) with mycosis fungoides and two of five patients (40%) with peripheral T-cell lymphoma. The median age at enrollment of the T-cell cohort was 61 (range, age 30–81), with no specific age. A recent series of seven patients demonstrated a high rate of response to pembrolizumab in natural killer/T-cell lymphoma, with CR in five of seven patients; however, only one patient was older than age 65.77 Of note, none of these studies performed age-specific subgroup analyses.

Finally, mediastinal gray-zone lymphoma lies intermediate between nodular-sclerosis classic HL and PMBCL, with overlapping clinical, histologic, and molecular features. In a report of three cases of refractory mediastinal gray-zone lymphoma that were successfully treated with anti–PD-1 therapy, two of them were in older adults: A 76-year-old man had a complete metabolic response after treatment with pembrolizumab and continues to be in remission on day 381 of treatment, and an 80-year-old woman had a complete metabolic response after treatment with nivolumab and continues to be in remission on day 161 of treatment.78

Non-Hodgkin Lymphoma: Anti–PD-L1 Therapy

Unlike PD-1, PD-L1 as a target has been less explored in patients with NHL. Forty-two patients with FL were recruited in a phase I/II trial with obinutuzumab/bendamustine plus atezolizumab as an induction regimen, followed by obinutuzumab plus atezolizumab as maintenance therapy.79 Patients enrolled had a median age at baseline of 57 (range, age 29–75), with seven patients age 65 or older (17%). With only one older patient included in the interim analysis of efficacy, the ORR was 80%, with a CR rate of 67% and a PR rate of 13%. We should wait until the final report to see whether there are differences among age subgroups. Other studies evaluating atezolizumab are still recruiting: atezolizumab in combination with obinutuzumab and tazemetostat in FL and DLBCL (NCT02220842), atezolizumab in combination with obinutuzumab and venetoclax in FL (NCT03276468), and atezolizumab monotherapy in relapsed and refractory HL (NCT03120676). Durvalumab has also been explored in lymphoma. Several trials evaluating different combinations are still recruiting, with no results formally published yet. All trials combining durvalumab with lenalidomide are on hold.
because of early reports of excess toxicity. Finally, avelumab is being explored in several trials in HL (NCT026034419) or in combination with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; NCT03244176) or with epigenetic modulators, bendamustine, or anti-CD137 in DLBCL (NCT02951156).

**CTL019 Chimeric Antigen Receptor T-Cell Therapy in Older Adults With Lymphomas**

In the ZUMA-1 trial (NCT02348216), among the 111 patients who were enrolled, axi-cel chimeric antigen receptor (CAR) T-cell therapy was successfully manufactured for 110 (99%) and administered to 101 (91%). The ORR was 82%, and the CR rate was 54%. With a median follow-up of 15.4 months, 42% of the patients continued to have an ongoing response, and 40% continued to have a CR. The OS rate at 18 months was 52%. The median age of the entire cohort was 58 (range, age 23–76), with 24 patients (24%) age 65 or older. In the DLBCL cohort, the median age at baseline was 58 (range, age 25–76), with 17 patients (22%) age 65 or older; in the transformed FL and PMBCL cohort, the median age was 57 (range, age 23–76), with seven patients (29%) age 65 or older. Response rates were consistent across key covariates, including age.

In the JULIET trial (NCT02030834), 28 adult patients with lymphoma received CTL019 cells. In the FL cohort (14 patients), the median age at baseline was 59 (range, age 43–72) and in the DLBCL cohort (14 patients) it was 58 (range, age 25–77). Of them, 18 of 28 had a response (64%); CR occurred in six of 14 patients with DLBCL (43%) and 10 of 14 patients with FL (71%). Sustained remissions were achieved, and at a median follow-up of 28.6 months, 86% and 89% of the patients with DLBCL and FL, respectively, were still responding. In the TRANSCEND NHL 001 trial, the first multicenter phase 1 trial of JCAR017 in relapsed/refractory B-cell NHL (NCT02631044), 74 patients were treated; of them, 69 in the DLBCL cohort had a median age of 61 (range, age 26–82). Best overall response, 3-month, and 6-month response rates were 75% (51 of 68), 49% (27 of 55), and 40% (14 of 35), respectively. The best overall, 3-month, and 6-month CR rates were 56% (38 of 68), 40% (22 of 55), and 37% (13 of 35), respectively. Among 16 double-/triple-hit patients with lymphoma, the best ORR was 81%, and the 3-month CR rate was 60%. Older patients were included in this trial, but subgroup analyses were not apparent.

**CONCLUSION AND FUTURE DIRECTIONS**

Immunotherapies, particularly the anti–PD-1 and anti–PD-L1 checkpoint inhibitors, have changed the therapeutic landscape for patients with advanced cancers across cancer type. These agents may offer alternatives to cytotoxic chemotherapy in a variety of settings, such as the frontline setting for patients with chemotherapy-ineligible locally advanced or metastatic bladder cancer, many of whom are older and/or with poor performance status and multimorbidity. Similarly, upfront immunotherapy strategies are being explored for patients with NSCLC and small cell lung cancer, as well as those with relapsed/refractory lymphomas, which may be more appealing for older adults. Combination strategies with radiation therapy for NSCLC and other solid tumors are still evolving. However, with additional combinations, particularly combined checkpoint blockade, there is a commensurate increase in intrinsic toxicity regardless of age. Patient selection among older adults for such evolving strategies remain of critical importance, especially for those trying to extrapolate and apply study data to the “real world,” in which older adults make up the majority of patients we see in the clinic.

Even among monotherapy strategies, the data on safety and efficacy of immunotherapies in older adults with cancer are limited. With the paucity of higher-level evidence-based data available, it seems that efficacy can be similar to that in younger patients, even though older patients tend to have more AEs in more nationally based studies, especially those with poorer PS. The hypothesis that can explain such clinical differences may be related to aging-related reductions in repertoire in the T-cell subsets and the pre-existing exhausted phenotype related to immunosenescence, which can be further affected by frailty and by prior chemotherapy.

With the integration of the evaluation of the aging immune system and the growing importance of the GA, a new concept of “comprehensive immune assessment” has been raised to be explored in older adults before they receive immunotherapies. Although toxicities among older adults treated with single-agent checkpoint inhibitors have been manageable when globally examined across these studies, to what extent the clinical benefit is seen in this population remains less clear. Moreover, data on the effect on hospitalization, health resource use, patient-reported outcomes, cost-effectiveness, and functional outcomes for older adults receiving immunotherapies remain lacking. Future research should evaluate the role of immunosenescence and its effect on such outcomes, how best to incorporate this into the GA framework, and how to use those data to guide the development of more prospective studies of older adults with cancer receiving immunotherapies.

**References**


Preventing Treatment-Related Functional Decline: Strategies to Maximize Resilience

Armin Shahrokni, MD, MPH, Koshy Alexander, MD, Tanya M. Wildes, MD, MSCI, and Martine T. E. Puts, RN, PhD

OVERVIEW

The majority of patients with cancer are older adults. A comprehensive geriatric assessment (CGA) will help the clinical team identify underlying medical and functional status issues that can affect cancer treatment delivery, cancer prognosis, and treatment tolerability. The CGA, as well as more abbreviated assessments and geriatric screening tools, can aid in the treatment decision-making process through improved individualized prediction of mortality, toxicity of cancer therapy, and postoperative complications and can also help clinicians develop an integrated care plan for the older adult with cancer. In this article, we will review the latest evidence with regard to the use of CGA in oncology. In addition, we will describe the benefits of conducting a CGA and the types of interventions that can be taken by the interprofessional team to improve the treatment outcomes and well-being of older adults.

Cancer is a disease that occurs more commonly in older adults. For example, the total number of cancers is projected to increase by 45% from 2010 to 2030 in the United States, driven largely by the growing number of older adults. By 2030, an estimated 70% of all cancers will occur among adults age 65 and older.

There is wide variation in the ability of patients of the same age to tolerate cancer therapy. Chronologic age alone is a poor descriptor of heterogeneity in the aging process and is an inadequate indicator to determine responses among older patients to cancer treatment. We need a systematic and evidence-based way to describe this heterogeneity to guide oncology treatment decisions. Geriatric conditions such as functional and cognitive impairments are frequently unrecognized or inadequately addressed in older adults. Rather than chronologic age, patients’ physiologic age or fitness level based on a “fit-to-frail” spectrum is more meaningful. Frailty is an important geriatric syndrome that is characterized by multisystem dysregulation, leading to decreased physiologic reserve and increased vulnerability for adverse health outcomes.

CGA involves the evaluation of the physical, psychosocial, and environmental factors that impact the well-being of older individuals. CGA is a multidimensional, interdisciplinary diagnostic process to determine the medical, psychological, and functional capabilities of an older adult, which should lead to the development of a coordinated and integrated plan for treatment and long-term follow-up to improve outcomes for older patients with cancer. Frail older adults may have multiple chronic conditions and may have difficulty maintaining independence. They may be more vulnerable to therapy toxicities and may not have substantial lasting benefits from therapy. CGA may be used as a tool to determine reversible deficits and devise treatment strategies to mitigate such deficits.

The CGA has been demonstrated to be superior to clinical judgment, even by experienced clinicians, when used to evaluate the fitness of older patients with cancer. Multiple studies have suggested a spectrum of benefits that arise from using CGA for older patients with cancer. For example, a prospective multicentric study on the large-scale feasibility and usefulness of CGA in oncology showed that CGA detected unknown geriatric problems in 51% of patients age 70 and older. When the physician was aware of the assessment results at the time of decision-making, geriatric interventions were planned for 25.7% of patients and the treatment decision was influenced for 25.3% of patients. CGA and its more abbreviated derivative commonly called geriatric assessment (GA) can be used in treatment decision-making by clinicians, helping to risk stratify patients prior to potentially high-risk therapy. GA and CGA have a role in predicting complications and side effects from cancer treatment. During the cancer treatment trajectory, CGA may be used as a tool to identify new deficits (e.g., a decline in functional activity levels) and devise treatment strategies to mitigate such deficits. A number of studies have shown the use of CGA in the estimation of survival. The online e-prognosis indices incorporate CGA.

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elements to estimate mortality risk. It may provide an effective approach to the management of pain and psychological status in the hospitalized older patient with cancer.

**PRACTICAL APPLICATIONS**

- Chronologic age alone is a poor descriptor of the heterogeneity in the aging process. Patients’ physiologic age or fitness level based on a “fit-to-frail” spectrum is more meaningful in charting out a cancer treatment trajectory.
- Geriatric assessment uncovers vulnerabilities that are not appreciated in routine oncology practice.
- Completion of geriatric assessment is feasible in the oncology clinical setting.
- Geriatric assessment can aid in personalizing risk prediction for toxicity of treatment and mortality.
- Nurses are key players in the care for older adults with cancer in the conduct of the CGA and the follow-up with interventions to address the issues identified.

In this article, we will discuss CGA domains and the feasibility of CGA and GA in research and daily practice. We also describe how geriatricians, nurses, and oncologists can use CGA and design and implement interventions to improve outcomes of older patients with cancer.

**COMPREHENSIVE GERIATRIC ASSESSMENT DOMAINS AND THEIR EVIDENCE**

CGA for the older patient with cancer includes an evaluation of functional status, comorbid medical conditions, cognition, nutritional status, psychological state, and social support, as well as a review of the patient’s medications. Table 1 describes domains of CGA and commonly used instruments. Table 2 describes the evidence on the importance of each CGA domain.

**FEASIBILITY OF COMPREHENSIVE GERIATRIC ASSESSMENT OR GERIATRIC ASSESSMENT**

Numerous studies have demonstrated the feasibility of incorporating brief, largely self-administered GA into both
TABLE 2. Current Evidence on Importance of CGA Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Before Treatment</th>
<th>During Treatment</th>
<th>After Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognition</strong></td>
<td>One in three seniors dies with a form of dementia in the United States today. The incidence of dementia doubles every 5 years after age 65. Because more than 50% of new cancers are diagnosed among those older than age 65, the overlap of cognitive dysfunction and cancer is a real problem.</td>
<td>Patients with a precancer diagnosis of dementia are less likely to receive invasive diagnostic testing as well as standard or curative intent treatments. Patients can have trouble remembering and following treatment instructions, delaying diagnosis of complications and decreasing adherence to prescribed primary and supportive treatments. Up to 75% of patients with cancer experience cognitive impairment during or after treatment of their cancer. For many patients (up to 35%), this persists for months or years after treatment.</td>
<td>Impaired cognition can result in substantial difficulties in understanding treatments and procedures, which is important in the process of obtaining informed consent. Both cancer and cancer therapies can negatively affect cognition, and older adults with preexisting cognitive impairment may be more susceptible to cognitive decline and delirium with therapy than younger patients. Post-treatment cognitive changes frequently include problems in attention, working memory, and executive function.</td>
</tr>
<tr>
<td><strong>Functional status</strong></td>
<td>Prevalence of functional disability increases with age. Performance status scores such as the ECOG and KPS are often used in oncology to estimate a patient's functional status. However, they tend to underestimate the degree of functional impairment among older patients.</td>
<td>Impaired functional status is associated with a higher risk of toxicity from chemotherapy. The CRASH score and the scoring system developed by the CARG include functional status criteria. Functional status decline is known to occur most frequently in the first year after diagnosis.</td>
<td>Patients who experience a persistent decline in physical functioning without recovery after treatment are at risk for functional decline and early mortality.</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td>Grip strength correlates with sarcopenia and has been shown to be associated with adverse outcomes for patients with cancer. Frequent comorbidities among elderly patients, such as cardiovascular disease, hypertension, diabetes, or dementia, influence the management of cancer.</td>
<td>Functional decline occurs in about one-third of older patients with cancer receiving chemotherapy. Decline in ADLs is strongly prognostic for overall survival.</td>
<td>An increased incidence of cardiac and/or pulmonary dysfunction is observed in cancer survivors.</td>
</tr>
</tbody>
</table>

Comorbidities may increase the risk of complications, modify cancer behavior, or mask symptoms. Cardiac events associated with chemotherapy may consist of mild blood pressure changes, thrombosis, EKG changes, arrhythmias, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, and CHF. Radiation therapy is associated with an increased risk of vascular disease, including coronary atherosclerosis.
**TABLE 2. Current Evidence on Importance of CGA Domains (Cont’d)**

<table>
<thead>
<tr>
<th>Domain</th>
<th>Before Treatment</th>
<th>During Treatment</th>
<th>After Treatment</th>
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<tbody>
<tr>
<td>Myocardial dysfunction and CHF</td>
<td>as a result of cancer treatment (anthracyclines, HER2 receptor antagonists) can</td>
<td>persist into survivorship[^59]</td>
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<tr>
<td></td>
<td>from cancer treatment</td>
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<td>Pulmonary fibrosis</td>
<td>can have an insidious onset and can present years after cancer treatment.</td>
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<td>Weight loss in patients with cancer</td>
<td>is an independent adverse prognostic factor and is associated with a lower</td>
<td>Nutritional status</td>
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<tr>
<td>nutrition and is associated with a</td>
<td>performance status.^[60]</td>
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<td>lower performance status.^[60]</td>
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<td>With the growing global obesity</td>
<td>Epithelial cell injury due to poor nutrition can lead to increased risk of</td>
<td>Malnutrition is prevalent up to 83% of older patients with cancer scheduled to</td>
<td>Malnutrition is associated with treatment complications and increasing</td>
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<tr>
<td>epidemic, there is consistent</td>
<td>cancer.^[61]</td>
<td>receive chemotherapy.^[62]</td>
<td>mortality among patients receiving chemotherapy, radiation therapy, or surgery.</td>
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<td>evidence that higher amounts of body</td>
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<td>fat are associated with increased</td>
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<td>risks of a number of cancers.^[61]</td>
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<td>Malnutrition is prevalent up to</td>
<td>About 40% of patients report anorexia after beginning treatment, and 67.2% of</td>
<td>Three years after surgery, 42% of patients who underwent laryngectomy and 50%</td>
<td>Chronic xerostomia that also impairs swallowing can occur up to 5 years</td>
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<td>83% of older patients with cancer</td>
<td>patients report at least one chemosensory alteration. Increased rather than</td>
<td>of patients who underwent pharyngolaryngectomy experienced long-term dysphagia</td>
<td>after treatment.^[71]</td>
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<td>scheduled to receive chemotherapy.^[62]</td>
<td>decreased taste sensitivities were more common.^[63]</td>
<td>leading to nutritional deficits.^[64]</td>
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<td>Malnutrition is associated with</td>
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<td>treatment complications and</td>
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<td>increasing mortality among</td>
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<td>patients receiving chemotherapy,</td>
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<td>radiation therapy, or surgery.^[65]</td>
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<td>Psychosocial status</td>
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<td>Social isolation, the lack of social</td>
<td>increased social isolation is a risk factor for poor tolerance of adverse</td>
<td>In a study of breast cancer survivors, patients with inadequate social support</td>
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<td>ties, is an independent predictor of</td>
<td>effects of cancer treatment.^[76]</td>
<td>experienced greater distress.^[77]</td>
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<td>mortality in the older population in</td>
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<td>general.^[72] For older patients with</td>
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<td>cancer, the prevalence of clinically</td>
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<td>substanstial depression ranges from 3%</td>
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<td>to 25%. Although the psychological</td>
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<td>impact of cancer among older adults</td>
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<td>is less adverse or similar compared</td>
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<td>with younger patients, organic mental</td>
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<td>disorders are more prevalent among</td>
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<td>the older group.^[73]</td>
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<tr>
<td>Patients with cancer and depression</td>
<td>increased social isolation is a risk factor for poor tolerance of adverse</td>
<td>Compared with patients without depression, the odds are three times greater</td>
<td>Among patients with hematologic cancer after stem-cell transplantation, major</td>
</tr>
<tr>
<td>are less likely to receive definitive</td>
<td>effects of cancer treatment.^[76]</td>
<td>that patients with depression will be noncompliant with prescribed treatments[^59]</td>
<td>depressive disorder predicts higher 1- and 3-year case mortality rates.^[59]</td>
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<td>treatment and hence experience worse</td>
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<td>survival compared with those without</td>
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<td>depression.^[74]</td>
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[^20]: 2018 ASCO EDUCATIONAL BOOK | asco.org/edbook
clinical trials and routine oncology practice. These studies have repeatedly and consistently shown that patients can complete the GA in 20 to 30 minutes, with minimal provider time (5–10 minutes) required to complete the components that are not self-administered (e.g., physical performance tests and a cognitive screen). Earlier studies used pencil-and-paper testing, but electronic completion of the GA is also feasible and equivalent to its forerunner. Given the extensive literature demonstrating its feasibility, there have been recent calls to reconsider the common refrain that GA is too time-consuming to incorporate into oncology practice. However, it is still unclear whether the CGA or GA can be implemented in the practices with limited resources.

**UTILIZING COMPREHENSIVE GERIATRIC ASSESSMENT TO DECREASE TREATMENT-ASSOCIATED TOXICITY IN CLINICAL PRACTICE**

Clinicians surveyed on factors that influence their treatment recommendations for older adults with cancer cited performance status as the most influential factor in their decision-making in both the adjuvant and palliative settings. It has long been recognized that comorbidities and performance status are independent and must be assessed separately, but the prevalence of functional limitations and frailty in individuals with a “good” performance status is underappreciated. In one cohort of almost 300 patients, 23% of patients assessed to be fit by the oncologist were categorized as frail using GA criteria. In a cohort of almost 800 older adults with solid tumors and a Karnofsky performance status of 80 or greater, more than two-thirds (69%) had at least one deficit identified by GA, including 23% with dependence in one or more instrumental activities of daily living (IADLs), 43% with nine or more medications, 18% with impaired physical performance on the Timed Up and Go test, and 7% with recurrent falls.

GA has demonstrated utility in predicting toxicity of cancer treatment, postoperative complications, and overall mortality. Improved risk stratification and risk prediction for these outcomes using GA may facilitate clinician recommendations and shared decision-making. Studies that have examined the relationship between GA and toxicity of chemotherapy are listed in Table 3. A systematic review showed that 49% to 64% of older adults experienced grade 3 or greater toxicity of chemotherapy and although most of the studies found associations between GA parameters and toxicity, studies were inconsistent in which geriatric domains were associated with toxicity. Domains found to be associated with toxicity included comorbidities, functional status/physical performance, decreased social activity, falls, hearing impairment, and nutrition. The range of domains found to be associated with toxicity underscores the necessity of the multidimensional appraisal of GA. Figure 1 demonstrates the Cancer and Aging Research Group risk prediction model with the risk of chemotherapy toxicity based on the patient’s score.

A number of large cohort studies have shown the utility of GA in predicting which older patients with cancer undergoing surgery are at greater risk for postoperative complications. In a cohort study of 460 older adults undergoing elective surgery for cancer, the PACE (Preoperative Assessment of Cancer in
TABLE 3.Prospective Studies of Geriatric Assessment to Predict Chemotherapy Tolerance

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Cancer</th>
<th>ADLs/IADLs</th>
<th>Physical Performance Measure</th>
<th>Comorbidities</th>
<th>Cognition</th>
<th>Medication</th>
<th>Depression</th>
<th>Geriatric Syndromes, including Falls or Frailty Measures</th>
<th>Social Status/Support</th>
<th>Nutrition</th>
<th>Association of GA Components With Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Massa et al[52]</td>
<td>75</td>
<td>Any</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Categorization of patients as fit, vulnerable or frail did not correlate with toxicity grade</td>
</tr>
<tr>
<td>Marinello et al[53]</td>
<td>110</td>
<td>Breast, lung, or colorectal</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Comorbidities associated with severe treatment toxicity</td>
</tr>
<tr>
<td>Puts et al[50]</td>
<td>112</td>
<td>Any</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Low grip strength predicted toxicity</td>
</tr>
<tr>
<td>Aaldricks et al[51]</td>
<td>202</td>
<td>Any</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Poorer nutritional status and cognition were associated with completing fewer cycles of chemotherapy</td>
</tr>
<tr>
<td>Hurria et al[50-56]</td>
<td>500 (development cohort); 250 (validation)</td>
<td>Any</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Risk prediction model associated with grade 3 or greater toxicity of chemotherapy (AUC of model was 0.72 in the development cohort and 0.65 in the validation cohort)</td>
</tr>
<tr>
<td>Extermann et al[5]</td>
<td>518</td>
<td>Any</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>IADLs associated with hematologic toxicity; ECOG performance status, nutrition, and cognition associated with nonhematologic toxicity</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Cancer</th>
<th>ADLs / IADLs</th>
<th>Physical Performance Measure</th>
<th>Comorbidities</th>
<th>Cognition</th>
<th>Medication</th>
<th>Depression</th>
<th>Geriatric Syndromes, Including Falls or Frailty Measures</th>
<th>Social Status / Support</th>
<th>Nutrition</th>
<th>Association of GA Components With Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luciani et al</td>
<td>648</td>
<td>Any</td>
<td>X (VES-13)</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Vulnerability by VES13 associated with both hematologic and non-hematologic toxicity</td>
</tr>
<tr>
<td>Hayashi et al</td>
<td>31</td>
<td>Any</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>Preserved ADL function associated with better tolerance of chemotherapy</td>
</tr>
</tbody>
</table>

Abbreviations: ADL, activities of daily living; IADLs, instrumental activities of daily living; GA, geriatric assessment; AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; VES13, Vulnerable Elders Survey–13.
the Elderly) investigators showed that fatigue, dependence in IADLs, and abnormal performance status were associated with postoperative complications; dependence in activities of daily living (ADLs) or IADLs and impaired performance status were associated with extended hospitalization. In a similar study of 328 older patients with any cancer undergoing resection, slower times on the Timed Up and Go, poorer scores on the American Society of Anesthesiologist scale, and impaired nutrition predicted major complications. In two separate cohorts of older patients with colorectal cancer undergoing resection, impairment in IADLs was associated with postoperative complications. A recent systematic review concluded that functional dependence, comorbidities, and frailty were geriatric domains most commonly associated with adverse postoperative outcomes in older adults with cancer. The role for GA in the older surgical patient will likely extend beyond risk prediction to support shared decision-making and enable prehabilitation to optimize an older adult’s health before elective surgery.

GA may also have a role for patients receiving radiation therapy, although data on its utility in predicting toxicity of radiation therapy have been less conclusive than in the chemotherapy and surgical setting. In a prospective cohort of 46 older adults with head and neck cancer, dependence in IADLs was not associated with tolerance of radiation but was associated with poorer recovery in health-related quality of life after radiation. Several other studies have found no association between geriatric domains and toxicity of radiation therapy. In a cohort of 178 patients undergoing radical radiotherapy for locally advanced prostate cancer, “CGA needs” (defined as one of the following: ADL/IADL dependence, residing in a residential care facility, or nine or more medications or falls in the past 6 months) were not associated with toxicity of radiation. In a cohort of more than 400 patients undergoing curative intent radiation, physical performance on the Timed Up and Go test and frailty using the G-8 scale were not associated with toxicity of radiation on multivariate analysis. Another study of more than 60 patients with various malignancies found no association between frailty and toxicity of radiation. Although studies to date have not shown a strong ability of GA to predict radiation toxicity, GA may uncover issues that require intervention and individualized supportive care for older adults undergoing radiation therapy.

GA or geriatric screening tools are predictive of mortality for older adults with cancer that is treated surgically, with radiation, and with chemotherapy. In a cohort of 339 older adults beginning a course of chemotherapy, male sex, advanced cancer, poorer nutrition, and slower time on the Timed Up and Go were associated with a greater risk of early mortality. Similarly, in a cohort of 190 older patients with tumors, gait speed below 0.8 m/s was associated with a fivefold greater risk of death within 6 months. In another cohort, it was not a physical performance test, but impairments in any of two of six domains (ADLs/IADLs, falls, polypharmacy, sensory impairments, or urinary incontinence or pain) in an abbreviated GA that was associated with survival. Finally, in a cohort of 131 patients who underwent elective surgery for malignancies, those who were both dependent in ADLs and had impaired time on the Timed Up and Go or those with impaired cognition
were at greater risk for mortality in multivariate analysis.\textsuperscript{116} Validation of such approaches to estimate an older adult’s risk of mortality after cancer treatment may allow more informed, personalized decision-making.

The potential of GA to improve prediction of toxicity and survival may allow physicians to tailor their recommendations to the unique health status of older adults. This is particularly important because older patients report that the most important factor in their treatment decision-making process is the oncologist’s recommendation.\textsuperscript{117} When oncologists are provided with results of GA, it influences their recommendations 20\% to 40\% of the time.\textsuperscript{118–120} With refined, individualized risk prediction, communication between patient and provider may be enhanced. In one recent pilot study of older adults with pancreatic or colorectal cancer and their surgeons, patients underwent a brief GA, which included query about goals and preferences. Surgeons underwent training in the components of the GA and techniques for shared decision-making. The surgeons were provided with results of the GA. Pre–post comparisons showed improvement in decision-making after the intervention.\textsuperscript{121} A large, cluster-randomized community-based study of the influence of GA on treatment decisions and shared decision-making in older adults considering systemic therapy is underway (NCT02107443).

Studies in which GA was used to direct treatment are emerging. Wright et al\textsuperscript{122} presented a quality improvement project in which they developed and used an algorithm incorporating GA and patient preferences. In a cohort of 24 older women with T1N0 estrogen receptor–positive breast cancer, decisions about nodal evaluation were influenced by 10-year life expectancy (calculated using GA), and adjuvant therapy was directed by both life expectancy and patient preferences.\textsuperscript{122} Rates of electing to forgo sentinel lymph node biopsies or adjuvant radiation increased with use of the algorithm. One large randomized trial utilizing GA to direct chemotherapy assignment was reported. The ESOGIA (Elderly Selection on Geriatric Index Assessment) trial randomized 494 patients with non–small cell lung cancer to a usual care arm, with the chemotherapy regimen determined by age and performances status, or to an experimental arm wherein chemotherapy was determined by fitness based on GA.\textsuperscript{123} Although the trial did not meet its primary endpoint of a 30\% improvement in treatment failure–free survival, overall survival was similar in the two groups, with lower toxicity in the group who received treatment based on GA, which many considered a proof of benefit of individualizing therapy based on GA.\textsuperscript{123}

**TEAM-BASED APPROACHES TO PERSONALIZED CARE FOR OLDER ADULTS: IT TAKES A VILLAGE**

A recent Delphi consensus framework for interventions guided by the GA can be used to identify appropriate interventions that nurses and other interprofessional team members can take to support older adults with cancer before, during, and after treatment.\textsuperscript{124} With the creation of an integrated care plan, it is crucial that one member of the health care team be responsible for coordinating care, following up on referrals and tests, and so forth. Cancer care coordination and cancer care navigation have been shown to improve care\textsuperscript{125} and other quality care outcomes. Nurses are well positioned to be the team member responsible for follow-up and care coordination with the older adult after the CGA.\textsuperscript{126,127} Table 4 presents a summary of the interventions that could be considered by the interprofessional team based on the different domains and guided by the consensus statement.\textsuperscript{128}

A core domain of the GA is management of current symptoms and comorbidities and medication review and management. Although the geriatrician, pharmacist, or nurse practitioner can perform the detailed medication review to optimize medications,\textsuperscript{129,130} nurses play a key role in assessing older adults’ medication use, beliefs, and adherence to medication. Evidence has shown that, for various reasons, up to one in two older adults may not adhere to their medication as prescribed.\textsuperscript{131,132} For example, older adults with cancer may have functional limitations, mobility limitations, financial limitations, depression, or cognitive impairment that can affect medication use.\textsuperscript{131,132} Although there are currently few effective adherence-enhancing interventions,\textsuperscript{133,134} nurses and other team members should take a multifaceted patient-centered approach.\textsuperscript{135} Nurses should assess and address the underlying reasons leading to suboptimal adherence with the older adult to identify which interventions may be most useful. Common problems include arthritis that may lead to problems opening pillboxes, not being able to pick up medications from the pharmacy, and forgetting to take the medication. Interventions that target these underlying issues can be identified. These might include having medications delivered by the pharmacy, using a dosette or blister pack, or involving a support person, application (“app”) software, or other memory aid(s) to remind the older adult to take the medication to facilitate adherence. Pharmacists are also in a good position to address suboptimal adherence.\textsuperscript{130,136,137} Patients may stop medications to reduce symptoms (e.g., of pain, weight gain, etc.) and the symptoms must be assessed and addressed.\textsuperscript{131,132,135}

Older adults with cancer often have other chronic conditions, and it is important to assess how they are managing these other diseases. Nurses can play a key role here by finding out, for example, what other specialists older adults are seeing, what other treatments they are receiving, what (if any) other care and support (e.g., nursing, occupational therapy/physical therapy or other rehabilitation services) they receive to manage their chronic conditions, and how their ability to complete their ADLs is affected.

Family physicians, nurse practitioners working in primary care, and geriatricians are key players in managing comorbidities. Nurses can teach self-management skills to empower older adults to manage their health and other conditions during cancer treatment through several tactics. These include educating older adults about changing medications needed during treatment, optimizing lifestyle choices to improve their health and well-being, and connecting

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older adults with community services for exercise programs. Nurses can also work with the team to assess whether co-morbidities are better managed by changes to medications (e.g., monitoring blood pressure to see if the hypertension/hypotension is better). Nurses can also facilitate communication between the geriatric oncology team and the primary health care team. Older adults taking many medications and experiencing dehydration, malnutrition, and electrolyte imbalances may be at higher risk of delirium. Nurses should address delirium

**TABLE 4. Proposed Interventions Based on CGA Impairments**

<table>
<thead>
<tr>
<th>Issues Identified in the CGA</th>
<th>Possible Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid conditions</td>
<td>Review comorbidities management by geriatrician/nurse practitioner in the cancer center in collaboration with the family physician</td>
</tr>
<tr>
<td></td>
<td>Nurses to provide support and education to facilitate self-management</td>
</tr>
<tr>
<td></td>
<td>Consider referral to social work to address barriers to optimal management (e.g., community)</td>
</tr>
<tr>
<td></td>
<td>Nurses to monitor symptoms and well-being over time to evaluate the new management plan because continuing/severe symptoms can impact well-being and adherence</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td>Perform a medication review to optimize the medications during cancer treatment</td>
</tr>
<tr>
<td></td>
<td>Nurses to provide education to the older adult and family members showing that a high number of medications is a risk factor for delirium and thus provide education for delirium prevention and early recognition</td>
</tr>
<tr>
<td>Suboptimal medication adherence</td>
<td>Assess and address the reasons for nonadherence</td>
</tr>
<tr>
<td></td>
<td>Pharmacists and nurses to support medication use</td>
</tr>
<tr>
<td></td>
<td>Consider occupational therapist referral for memory aids and support for medication adherence in the home (e.g., in case of functional limitations impacting adherence)</td>
</tr>
<tr>
<td>Falls</td>
<td>Nurses to assess fall history, fear of falling, balance, and gait difficulties</td>
</tr>
<tr>
<td></td>
<td>If any of these issues present, team to conduct a comprehensive fall assessment and dependent on the assessment interventions to be implemented</td>
</tr>
<tr>
<td></td>
<td>Consider occupational therapists and physical therapy referrals for environmental assessment to prevent falls in the home and arrange assistive devices/technology for in the home</td>
</tr>
<tr>
<td></td>
<td>Consider physical therapist referral for a tailored exercise plan to increase balance and strength</td>
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<tr>
<td></td>
<td>Nurses to provide ongoing monitoring</td>
</tr>
<tr>
<td></td>
<td>Consider calcium and vitamin D supplementation</td>
</tr>
<tr>
<td>Substantial weight loss/poor</td>
<td>Review weight history/weight loss and appetite and food intake</td>
</tr>
<tr>
<td></td>
<td>Consider referral to a diettian in the case of malnutrition</td>
</tr>
<tr>
<td></td>
<td>Assess and develop a management for symptoms that interfere with intake (e.g., pain in mouth)</td>
</tr>
<tr>
<td></td>
<td>Address constipation/diarrhea and nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Nurses to provide patient education about nutrition and hydration to all older patients with poor appetite/no weight loss</td>
</tr>
<tr>
<td></td>
<td>Consider a referral to food delivery programs (e.g., Meals on Wheels), grocery delivery services, and support for meal preparation</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Nurses should evaluate the social support available and what is needed during the treatment (ongoing monitoring)</td>
</tr>
<tr>
<td></td>
<td>Provide education about healthy lifestyles such as smoking cessation, exercise, and diet to reduce the risk of further cognitive decline</td>
</tr>
<tr>
<td></td>
<td>Discuss optimization of vision and hearing</td>
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<tr>
<td></td>
<td>Referral to social work for supports at home for the older adult’s safety and avoidance of caregiver burnout</td>
</tr>
<tr>
<td>Delirium prevention and recognition</td>
<td>Nurses to provide patient education to older adult and caregivers about delirium prevention and early recognition</td>
</tr>
<tr>
<td>Depression</td>
<td>Nurses should provide support and foster hope</td>
</tr>
<tr>
<td></td>
<td>Nurses should assess social support network and ways to increase the supports available</td>
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<tr>
<td></td>
<td>Nurses to provide patient education on treatment of depression (sleep hygiene and physical activity)</td>
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<tr>
<td></td>
<td>Nurses to consider referral to social worker/psychology services for increasing problem-solving skills and counseling</td>
</tr>
<tr>
<td></td>
<td>Monitor for the risk of suicide</td>
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</tbody>
</table>

Abbreviation: CGA, comprehensive geriatric assessment.
prevention with older adults and their caregivers with several strategies, including patient education about the sleep-wake cycle, adequate pain management, management of constipation/diarrhea during treatment, adequate nutritional intake and hydration, prevention and management of nausea and vomiting, cognitive stimulation, adequate vision and hearing, and physical activity. Nurses should use screening tools for delirium and discuss with the older adult and their caregiver the signs of delirium for early identification. The most commonly used tool is the Confusion Assessment Method.

Complicating matters, those with cognitive impairment are at higher risk of delirium. Cognitive impairment affects cancer treatment delivery and prognosis, but cancer treatment can also cause cognitive impairment. It is thus important that the geriatric oncology team clearly communicates the results of the CGA and develops a plan to support the older adult with cognitive important during the treatment. Nurses should assess the social support available to the older adult during the treatment. Referal to an occupational therapist could help identify strategies in the home that the older adult or caregiver can use to adapt to the challenges (e.g., through providing memory aids in the home for daily activities). Nurses should discuss lifestyle such as engaging in mental and physical activity and engaging in social interactions; smoking cessation and optimizing vision and hearing may reduce the risk of further cognitive decline. It is also important for nurses to assess caregivers’ health and well-being to support the caregiver and avoid caregiver burnout. A referral to a social worker may be considered for additional support at home (e.g., professional and community services such as locally available volunteer services for respite for the caregiver).

Older adults with cancer may be at higher risk for falls and injurious falls. It is important that with the CGA, nurses assess whether the older adult has had a fall in the previous 12 months and, if yes, review the circumstances under which the patient fell: Was the patient running for the bus and tripped? Did the patient get dizzy and fall while going to the bathroom at night? If the older adult reports multiple falls, a fall for which medical attention was needed, or a fear of falling or has balance and gait abnormalities, a comprehensive fall risk assessment may be considered to identify fall risk factors and develop a management plan. A recent meta-analysis by Tricco et al reported that the most effective intervention for reducing falls is exercise alone or exercise in combination with other interventions (including improving vision, environmental assessment and modification, case management, and calcium and vitamin D supplementation). An occupational therapist can assist with environmental interventions to address home hazards such as slippery floors, loose rugs, lack of handrails/grab bars in bathrooms, staircase changes, and safer transfers. Occupational therapists can help older adults develop a plan for completing daily tasks, especially when they are fatigued, so that they can perform these tasks while conserving as much energy as possible.

Nurses can also play a valuable role in fall risk factor reduction by providing patient education about fall prevention (sitting up on the edge of the bed before getting out of bed, removing loose carpets, proper use of assistive devices, safety at home, what to do in case of falls, etc). Exercise may also help manage cancer fatigue. If the older adult has comorbidities, referral to a physical therapist may be considered to develop an exercise plan tailored to the older adult, taking into account the existing functional status limitations. However, it is important that all team members are cognizant of the language used to discuss fall prevention strategies. In a synthesis of qualitative research of perceived fall risk in older adults, Gardiner et al reported that just being perceived as at risk for falls is felt to be threatening and they recommended discussing fall risk in terms of a proactive approach toward living well and healthy behavior.

Weight loss or poor appetite may also be identified during the CGA. Nutritional status affects prognosis for patients with cancer and can also affect treatment toxicity. Poor nutritional intake and weight loss for older adults with cancer can have several causes, including limited ability to obtain and prepare meals as a result of cognitive and functional limitations, mobility impairment, and financial limitations, the cancer itself (malabsorption/obstructions and fatigue), and the treatment (nausea/vomiting, constipation/diarrhea, mucositis, taste alterations, and pain).

Malnutrition is common in community-dwelling older adults; thus, many patients may already be in need of nutritional interventions before they begin cancer treatment. It is important that nurses assess to identify the patient’s weight history and possible reasons for weight loss or poor nutritional intake. Nurses should consider referral to a dietician for a nutritional assessment and nutritional interventions such as oral supplements (including protein supplements) and exercise. In the case of inadequate intake as a result of functional or cognitive impairment, nurses should consult with the caregiver to determine whether options such as grocery delivery, meal delivery programs (e.g., Meals on Wheels), or caregiver-supported meal preparation are available.

Depression is common in older adults: 10% to 15% of community-dwelling older adults have considerable clinically relevant depressive symptoms. Depression is also common in oncology. It is important for nurses to monitor the symptoms and suicide risk, because increased age, depression, multiple comorbidities, pain, functional impairment, lack of social support network, and hopelessness are all risk factors that are present among many older adults with cancer. Nurses should consider a referral to psychosocial oncology services or a social worker for counseling and interventions aimed at improving problem-solving abilities. Nurses should educate patients and their families about the importance of maintaining health and sleep hygiene and the benefits of exercise. However, a substantial proportion of older adults live alone and may have a small support network. Nurses should assess the social support system for emotional support and build a therapeutic relationship focusing on enhancing the older adult’s coping strategies.
skills and ways to foster hope. A social worker may assist in evaluating locally available support services in the community, such as volunteers, peer supports, and activity and exercise programs.

Cancer is a complex disease with often difficult treatments. Older adults with cancer often have one or more chronic conditions in addition to cancer and may have already complex medication regimens. CGA and management is an important tool in managing the health of this vulnerable population, and nurses and the other members of the interprofessional team play a key role in its delivery.

**HOW TO INCORPORATE GERIATRICS CARE INTO CARE FOR OLDER ADULTS WITH CANCER?**

In the previous sections, we described the domains of CGA and their instruments. We also discussed the association between CGA domains and cancer outcomes. We then explained the interventions that can be performed by allied healthcare professionals based on CGA findings. In this section, we describe the models that can be used to incorporate geriatric care into routine care of older adults with cancer.

**Incorporating Geriatric Principles in Oncology Training**

By 2030, approximately 70% of patients with cancer will be older than age 70. As a result, it is critical that oncologists are introduced to domains of CGA and its importance. They should also learn basic interventions that can be performed in fast-paced clinics. Different courses and programs are available via ASCO or the International Society of Geriatric Oncology.

**Shared Care Model**

In this model, oncologists and geriatricians share the care of older adults with cancer. The model emerges from successes in nononcologic setting. For example, a systematic review showed that shared postoperative care between geriatricians and orthopedic surgeons decreases postoperative morbidity and mortality substantially. The model can be applied in different phases of cancer care from preoperative evaluation to end of life or cancer survivorship. Memorial Sloan Kettering Cancer Center has described the implementation of a shared care model across the cancer continuum. In this model, the role of the geriatrician changes over time. In early phases of treatment, the model optimizes the fitness of older patients with cancer, while near the end of life, it focuses on introducing patients to palliative care and the hospice setting. The advantage of such a model is the guarantee for the proper GA and interventions by the geriatrician. However, the model is resource intensive, and with the limited number of geriatricians in the United States, it may not be scalable. The shared care model also requires clear allocation of tasks assigned to each discipline in the care of older patients with cancer. For example, who is responsible for managing new-onset hypertension for a patient who has begun taking tyrosine kinase inhibitors?

**Geriatric Oncology Consultation Model**

In this model, the geriatric oncology consultation clinic is attended by a geriatrician or an oncologist with training or expertise in geriatrics. Major activities of this clinic usually include performing CGA and recommending proper interventions based on identified problems in the CGA. Mostly, the execution of the recommendation will be deferred to the primary oncology team. The consultation model is not as resource intensive as the shared care model and thus has potential for scalability. This model is feasible to be implemented. Additional studies are ongoing to provide evidence of its effectiveness in improving outcomes of older patients with cancer. It remains to be seen whether Oncology Care Model and quality-based payment options will embrace the utility of GA and CGA in the care of older adults with cancer.

**CONCLUSION**

GA is a mechanism to summarize the heterogeneity of health status of older adults and is feasible to implement in the oncology setting. GA can uncover vulnerabilities that are under-recognized if only performance status is assessed, has utility in predicting toxicities of treatment or mortality, and may ultimately improve decision-making for older adults with cancer. Multidisciplinary interventions, including nursing-led interventions, informed by the results of CGA hold promise to improve the care of the older patient with cancer. A number of models of care are emerging to effect this multidisciplinary care.

### References


GLOBAL HEALTH
Cancer Care for Refugees and Displaced Populations: Middle East Conflicts and Global Natural Disasters

Nagi S. El Saghir, MD, FACP, FASCO, Enrique Soto Pérez de Celis, MD, MSc, Johny E. Fares, MD, and Richard Sullivan, MD, PhD

OVERVIEW

Conflicts and natural disasters can cause major disruptions to people’s lives. Media and news agencies usually focus on immediate consequences of these events, including loss of life and injuries, environmental and property destruction, and relief efforts. In this article, we will examine the effects of conflicts (focusing on in the Middle East) and global natural disasters on patients already diagnosed with cancer and on those who are diagnosed with cancer during and in the immediate aftermath of these events. We will review the limited literature, provide situational analysis, and discuss medical relief efforts, governmental readiness, and the role of United Nations agencies and international nongovernmental organizations. We will also discuss treatment of patients with cancer in the context of prolonged displacements and limited resources.

Conflicts and natural disasters can cause major disruptions to people’s lives. Media and news agencies usually focus on immediate consequences of these events, including loss of life and injuries, environmental and property destruction, and relief efforts. In this article, we will examine the effects of conflicts (focusing on in the Middle East) and global natural disasters on patients already diagnosed with cancer and on those who are diagnosed with cancer during and in the immediate aftermath of these events. We will review the limited literature about noncommunicable diseases (NCDs), provide situational analysis, and discuss medical relief efforts, governmental readiness, and the role of United Nations agencies and international nongovernmental organizations. We will also discuss treatment of patients with cancer in the context of prolonged displacements and limited resources.

CONFLICTS, INJURIES, AND POPULATION DISPLACEMENT IN THE MIDDLE EAST

Conflicts that escalate into violence are a major cause of people’s displacement from their residences and even their countries, as they may need to search for shelter and safety outside of their home country. Use of modern weaponry also causes massive destruction and inflicts severe human injury. According to the United Nations High Commissioner for Refugees (UNHCR), we are now witnessing the highest levels of human displacement to date. There are approximately 65.6 million refugees and displaced people worldwide.1 The UNHCR defines refugees and displaced people as those who are forced to leave their homes as a result of conflict, persecution, generalized violence, or human rights violations. Over the last several decades, the international community has faced many refugee crises, during which public health issues, such as infectious diseases and malnutrition, were managed as part of relief efforts. However, NCDs are often not well targeted in such circumstances, and they are not given as much importance as the other diseases during crises management and resolution.2

In the Middle East, millions of Palestinians have lived as refugees and displaced persons since the 1948 war and subsequent armed conflicts.3,4 Hundreds of thousands of Iraqis were displaced during the 2001 invasion of Iraq and the subsequent wars and terrorism that followed. The Syrian conflict, which started in 2011, has caused one of the most devastating human crises; millions of refugees and displaced persons have flowed into neighboring Lebanon, Jordan, Turkey, as well as Europe and the many other countries in the world. The latest conflict in Yemen is another major devastating event, with many Yemeni civilians remaining displaced in their own country. Lebanon has also suffered human displacement because of its own civil war in the 1980s. In addition to direct war-related deaths and injuries, displaced people may have pre-existing diseases, develop new diseases, and require health care, sanitation, infrastructure, and manpower. Lebanon hosts the largest number of Syrians refugees in proportion with its national
population, 183 per 1,000. Lebanon is also presently the destination of tens of thousands of Iraqis seeking medical care. The American University of Beirut Medical Center has treated those suffering from war casualties, victims of car bombs and terrorist explosions, as well as refugees and displaced people from the wars and conflicts in the Middle East during the past several decades.

Refugees and Displaced People With Cancer in the Middle East

Refugees and displaced people may see their cancer treatment interrupted, or they may develop a new cancer while they are in host countries. They often present with advanced disease and suffer more complications. These patients have poor outcomes because of poor hygiene and living conditions, as well as the limited health education, limited access to care, and limited resources available to them. They are usually unfamiliar with the health system in their asylum countries, and they are not enrolled in screening programs. A study done in Turkey, which receives the highest crude number of Syrian refugees, showed that the most common cancer type among refugees was breast cancer, and the majority of patients were diagnosed at an advanced stage. Unlike refugees displaced from conflicts in Africa, where endemic and epidemic infectious diseases and malnutrition are the main health crises, Syrian refugees are more affected with chronic and costly diseases, such as hypertension, diabetes, heart diseases, and cancer. In the aftermath of conflicts, countries may have infrastructures destroyed and manpower displaced, which causes patients with cancer to seek treatment outside of their home countries.

Cancer in displaced people: statistics from Syria. War in Syria has caused the worst humanitarian crisis of the 21st century, as declared by the UNHCR. It has resulted in the displacement of over 12 million people inside and outside Syria and destruction of large numbers of hospitals, clinics, laboratories, pharmaceutical factories, and infrastructures crucial to oncology care. According to the World Health Organization (WHO), at the end of 2017, 45% of public hospitals were reported damaged, with 15% fully damaged and 30% partially damaged. Forty-nine percent were reported fully functioning, 25% of hospitals were reported partially functioning, and 26% were reported nonfunctioning. Diagnostic imaging modalities and radiation therapy are not available in the majority of medical centers in Syria, making it very hard for the physicians to follow the universal guidelines in diagnosis and treatment. Many physicians and medical personnel have either died or left the country. Physicians for Human Rights reported that 15,000 doctors had left the country in 2015.

Patients with cancer cannot get proper treatment, neither inside Syria nor in neighboring host countries. According to WHO’s Health Resources and Services Availability Monitoring System, only 23% of functional public hospitals in Syria provided cancer treatment services. Only 46% of patients with cancer in Syria completed radiotherapy treatment without interruption, and 55% of them completed systemic therapy/chemotherapy without interruption. The mean nurse-to-physician ratio is 1.71:1 in 94 surgical hospitals in Syria. This ratio is almost half of the worldwide recommended ratio, which is 3:1 to 4:1, and is much lower than the 5:1 ratio recommended in the Sphere Handbook for minimum standards in disaster responses.

International Relief Efforts and Patients With Cancer in the Middle East

Although international agencies and volunteer organizations provide various kinds of needed medical support, in many host countries, the expenses of treating patients with cancer are often not covered because they are designated

PRACTICAL APPLICATIONS

- Conflicts and natural disasters cause destruction, acute bodily injuries and displacement of people from their own homes. Worldwide, there are tens of millions of refugees and displaced people in their own or host countries. In addition to general medical and surgical problems, they may either have their cancer treatment interrupted or develop new cancers.
- Host countries, United Nation organizations, UNHCR, International Red Cross, and various humanitarian organizations bear extensive burdens and alleviate great human sufferings but offer limited coverage for the management of cancer because of limited resources, other more urgent priorities, and high costs.
- In addition to increasing budgets for relief organizations and asking that cancer treatment be covered like other NCDs, implementation of resource-stratified guidelines may help provide much needed care for early diagnosis and treatment of cancer in large refugees and displaced people where full resource-intensive care is not possible.
- Hurricanes, flooding, drought, earthquakes, volcanic eruptions and mass movements represent enormous challenges for both high- and low-income countries that have varied degrees of preparedness. The United Nations adopted the Sendai Framework for Disaster Risk Reduction, which aims at reducing disaster risk, protecting persons, and strengthening the resilience of communities and countries. The Sendai Framework focuses on providing information for patients with cancer and caregivers, ensuring continuity of care, identifying vulnerable patients, including cancer care in rapid response teams, strengthening the resilience of the health care infrastructure, rebuilding back, and seeking international cooperation.
- With the growing burden of cancer and mass displacement of populations worldwide, we find a particularly neglected community of cancer patients who struggle to get medical care. Considering the present disorganized and underfunded approach, the global health community must change its perceptions, vision and strategy to tackle this issue. United Nations and nongovernmental organization roles are essential and should be highly supported.
as having too poor of a prognosis and/or treatment is financially too costly.2,17 Countries that host the highest number of refugees, such as Lebanon and Turkey, lack cancer surveillance programs that track the number of refugees with cancer, which makes it impossible to know how many of these patients are requiring treatment and not receiving it because of limited resources.7 The UNHCR is facing serious limitations to support those patients and provide them with the treatment they need. This is due to the limited funding for humanitarian emergencies since the beginning of the Syrian crisis. The UNHCR in Lebanon is facing an 83% deficit in funding.18 Because of the limited resources and the overwhelming needs, the UNHCR selectively funds expensive treatment based on the decision of a UNHCR Exceptional Care Committee, which relies on several criteria to select the cases that most deserve to receive health care coverage. One of these criteria is disease prognosis.2 For example, out of 511 applicants for expensive cancer treatment in Jordan, the Exceptional Care Committee denied care for more than 50% because of poor prognosis.2 However, results from a recent survey from The Johns Hopkins Center for Humanitarian Health noted a change of funding for cancer treatment for refugees in Lebanon and Jordan in 2016.19

Experience at the American University of Beirut Medical Center. In Lebanon, the Ministry of Public Health reported that in 2016, public hospitals had accumulated a deficit amounting to $15 million since the onset of the Syrian crisis.20 This indicates that the large influx of refugees and displaced people into a neighboring country may cause a significant negative impact on the health care system and its already-limited resources. A report on the effect of refugees from Syria and Iraq on breast cancer incidence in Lebanon showed a substantial 37.6% increase in breast cancer cases. At the American University of Beirut Medical Center, 41% of patients with breast cancer seen in 2015 were Iraqi and Syrian. The percentage (24%) of Iraqi patients who presented with metastatic breast cancer was higher than the percentage (15%) of the Lebanese patients. In addition, the percentage of Iraqi patients with breast cancer who were screen-detected was only 4% compared with 28% for the Lebanese patients with breast cancer.6 Advanced disease at presentation has also been noted in studies of refugees from Turkey.9,21

The Children’s Cancer Center of Lebanon at the American University of Beirut Medical Center, which is affiliated with St. Jude Children’s Research Hospital of Memphis, Tennessee, provides treatment of a large number of Syrians refugees and other displaced patients from the region. Since 2013, it has received humanitarian funds for displaced patients and was offered complete modern, unrestricted management for 126 displaced Syrian and Palestinian children with different types of cancer.21

Cancer Awareness, Early Detection, and Screening for Refugees and Displaced People
Countries of asylum should keep national cancer registries updated to achieve better cancer surveillance and allow forecasting of crises so that aid from international organizations can be requested beforehand. Public awareness and information about how, where, and when to seek medical attention should be made more available to refugees in asylum countries. This could be achieved by improving communication between the health care system and the refugees through publicity and awareness campaigns. Detecting cancers at early stages would lead to better prognoses and less-costly treatment.7,17

Financial Coverage and Resource-Stratified Guidelines for Refugees and Displaced People
One of the main reasons for the failure of supporting refugees with cancer is the misconception that all types of cancers have poor prognoses and that all cancer treatments are expensive. This is not always the case. The United Nations as well as other agencies and host countries may apply resource-stratified guidelines to manage refugees with cancer where required. A patient with a breast cancer may be treated with mastectomy and tamoxifen rather than left untreated. We should apply the principle of doing the best we can with the resources that we have.17 Patients can be treated with a limited workup, fine-needle aspiration, basic surgery, cheaply priced chemotherapy, and hormonal therapy. As for financing of medical and surgical treatment of refugees and displaced people with cancer and other diseases, the UNHCR and other humanitarian agencies need and should be allocated more money and resources. The United Nations and humanitarian agencies should be enabled to ask governments that fuel wars and conflicts to pay for resulting damages and medical expenses. Allocation of more financial resources to the UNHCR and other humanitarian agencies would help cover more patient treatment.

CANCER CARE IN THE FACE OF DEVASTATION: MEANINGFUL RESPONSE TO NATURAL DISASTERS
Natural disasters, such as hurricanes, flooding, drought, earthquakes, tsunamis, volcanic eruptions, and mass movements, can occur at any time and in any location in the world. The loss of human life and infrastructure caused by natural disasters can exert a heavy toll on the well-being of people and communities, and greatly damage their health, cultural heritage, socioeconomic assets, and ecosystems.23 Between 1994 and 2013, 6,873 natural disasters were recorded, which claimed a total of 1.35 million lives. An average of 218 million people were affected by natural disasters every year during that timeframe.24 The most common natural disasters during that period were climate-related events, which accounted for approximately 91% of worldwide disasters. On the other hand, geophysical disasters (e.g., earthquakes and tsunamis) were the most deadly, accounting for 55% of disaster-related deaths.24 Natural disasters represent an enormous challenge to the organization, preparedness, and resilience of health care systems. Immediately after natural disasters strike a community, the response is mostly geared toward providing
acute care for the injured. However, when critical health care infrastructure is destroyed, access to treatment and medication for people with chronic NCDs, such as cancer, is jeopardized. Disasters may also lead to an increase in other health risks, such as infections, which may disproportionately affect frail individuals, such as older adults and patients with treatment-related immune suppression.

**The Impact of Natural Disasters on Cancer Care**

Most of the data regarding the effect of natural disasters on cancer care comes from the aftermath of Hurricane Katrina in the United States in 2005 and from the earthquake and tsunami in Japan in 2011. After the destruction caused by Hurricane Katrina, for instance, New Orleans lost 80% of its hospital capacity and 75% of its safety net clinics. Furthermore, 800,000 people (mostly from underserved populations) were displaced because of flooding and housing damage. Cancer care was directly affected, with discontinuation of oncology services at public hospitals that lasted up to a year. Sixty-eight percent of all medications dispensed for hurricane evacuees were for the treatment of NCDs, and, among families living in affected communities, almost 5% of adults reported having a cancer diagnosis. Data from the National Program of Cancer Registries showed that, in the states of Alabama and Louisiana, up to 24,000 individuals with a recent diagnosis of cancer may have been affected or displaced by Katrina. Displaced patients, as well as those living in communities with damaged communication and transportation infrastructure, had difficulties obtaining access to timely care. Among patients with head and neck cancer seen in the New Orleans–Baton Rouge area, for example, those with low availability of transportation, as well as those who perceived a lack of access to oncology care, were more likely to have diagnostic delays. The most frequent barriers encountered by health care providers after Hurricane Katrina were inadequate medical information (e.g., inaccessible medical records) and financial constraints as a result of the high number of uninsured patients seeking care.

The 2011 earthquake and ensuing tsunami and Fukushima Daiichi nuclear reactor meltdown produced one of the biggest disasters in the history of Japan. The region hit by the tsunami lost 10 hospitals, 83 clinics, and 10% of available hospital beds. Furthermore, as a result of the nuclear emergency, over 80,000 people were ordered to evacuate the area, leading to a 20% decrease in the number of available health care providers, who fled to other regions of Japan. An analysis of the mortality statistics in the affected area showed that the risk of death as a result of causes other than trauma significantly increased in the month after the earthquake but returned to normal after 3 months. This increase in mortality was particularly seen among women older than age 85. An increase in cancer-specific mortality was also found in octogenarians during the first month after the disaster, which may be explained by the fact that these patients were more vulnerable and/or unable to evacuate the area. However, it is important to mention that cancer-specific mortality rates stabilized quickly and remained stable in the 5 years after the disaster. Although mortality rates did not change significantly, the diagnosis and treatment of patients in the area may have been affected, as shown by a study demonstrating that 33% of patients with breast cancer treated in the 5 years after the earthquake experienced treatment delays, compared with 19% before the disaster.

**Preparing for Natural Disasters**

Both Hurricane Katrina and the East Japan earthquake affected high-income countries with resilient health care systems. In Japan specifically, the lessons learned from the 1995 Kobe earthquake led to a coordinated and swift response that was able to successfully stabilize the situation in a short period of time. The Japanese Ministry of Health deployed more than 300 disaster medical assistance teams within 24 hours after the 2011 earthquake. Additionally, telecommunications were rapidly restarted, allowing for the transfer of medical records and for rapid dissemination of information regarding needs at the local and regional level using the internet.

Unfortunately, most natural disasters occur in low-income countries with vulnerable health care systems, where a coordinated response is less likely to occur because of economic and structural constraints. To address these disparities, the United Nations adopted the Sendai Framework for Disaster Risk Reduction (www.unisdr.org/we/coordinate/sendai-framework), which aims to reduce disaster risk, protect persons, and strengthen the resilience of communities and countries.

Several of the general guidelines included in the Sendai Framework, as well as some of the lessons learned during past disasters, can be applied to cancer care in both high and low-income countries:

1. **Providing information for patients and caregivers.** Ensuring access to information regarding where to obtain care in case of an emergency can represent a lifeline for patients. ASCO offered resources to patients affected by Hurricanes Harvey, Irma, and Maria in 2017, and the American Cancer Society has developed a series of recommendations for patients with cancer facing natural disasters. These recommendations were translated into Japanese and distributed among evacuees and at health care centers in the aftermath of the 2011 East Japan earthquake. Other novel technologies, such as social media, have also been used to disseminate information and to obtain data and optimize disaster response.

2. **Ensuring continuity of care.** One of the main issues faced by Hurricane Katrina evacuees was the lack of information regarding current and past medical history. Ensuring remote access to medical records and providing patients with “grab-and-go” copies of their basic disease-related information (e.g., the ASCO/National Cancer Institute wallet card) is an essential component of disaster preparedness.
3. Identifying vulnerable patients. Older adults, particularly those who are socially isolated and/or dependent in their activities of daily living, are highly vulnerable after natural disasters. Mapping systems should be used to identify older adults with cancer, and a specific plan for older patients, including dedicated shelters, should be instituted. Patients who need life-supporting interventions, such as hemodialysis, should also be identified and promptly evacuated to areas where these are available. Finally, patients who are in need of palliative care and those who have complications of cancer treatment should have the highest priority. A good example of a system for disaster surveillance is the Institute of Epidemiology, Disease Control, and Research in Bangladesh, which rapidly assesses the functioning of the health system after natural disasters.

4. Including cancer care in rapid-response teams. WHO recommends setting up mobile clinics equipped to treat NCDs, training first responders to implement the WHO package of essential NCD interventions, and including essential NCD medicines in emergency health kits. Among the medications included in WHO’s NCD essential list, those used to treat pain (such as morphine and nonsteroidal anti-inflammatory drugs) and those that can treat adverse effects of chemotherapy (such as antiemetics, laxatives, and steroids) can be particularly useful for patients with cancer.

5. Strengthening the resilience of the health care infrastructure and “building back better.” Hospitals, clinics, and other health care facilities are critical infrastructure, and a coordinated effort must be made to ensure their safety, effectiveness, and operation during and after disasters. Building codes should be strictly followed when health care facilities are planned in areas at risk, and damaged health care infrastructure should be rebuilt following the highest structural standards.

6. International cooperation and global partnership. Disasters disproportionately affect low-income, vulnerable countries that may not have the necessary resources to launch an effective response, such as treatment of patients with cancer or rebuilding damaged infrastructure. International organizations, such as ASCO, could potentially play a role by deploying specialists in oncology or in palliative care to assist patients affected by natural disasters in developing nations.

HEALTH CARE FOR REFUGEES AND DISPLACED PEOPLE: SITUATIONS ANALYSIS IN PARTICULAR COUNTRIES

Cancer represents a very significant social and economic burden of disease in the tens of millions of refugees and displaced people worldwide. The current level of attention and resources directed toward refugee cancer care are highly inadequate. We will highlight this neglect by presenting a brief economic analysis of the burden of cancer in a selected refugee population. We will also discuss the role of the United Nations and nongovernmental organizations. The population investigated is the 4.74M Syrian refugees currently residing in Jordan, Turkey, and Lebanon, and the costs estimated are for the provision of cancer-specific services. The experience of health care for refugees in Lebanon is perhaps the most complex and also the most substandard. Again, there is very limited information directly available on the experience of patients with cancer, but the overall level of accessible (affordable) health services is low. Primary health care is run by nongovernmental organizations and has user fees attached, and, to access secondary or tertiary care, refugees have to be funded by UNHCR on a case by case basis, as the tertiary health system in Lebanon is totally privatized. The result is that often only life-threatening conditions are financed, and the rest is left to the refugee population to arrange. In Turkey, it is difficult to find relevant information. It is possible that this is linked to the fact that the Turkish government is in the lead for the refugee response, and the United Nations agencies are marginalized. However, what is known is that all registered refugees are formally eligible to the same rights of access to health care as Turkish citizens, which means health care is heavily subsidized by the government insurance scheme.

In Jordan, originally the Jordanian government had provided free health care to all registered refugees—to the same standard as insured Jordanians. However, with the system under immense strain, the government abruptly stopped this support in November 2014. To fill the gap, a hybrid system was put in place, whereby, theoretically, nongovernmental organizations and private donors would fund access to Ministry of Health secondary and tertiary care, and primary care would be covered more directly by nongovernmental organizations. Unfortunately, this policy only applied to registered refugees living inside camps. So the approximately 500,000 registered refugees that were living outside of camps (about 83% of the total) were not eligible for support, and instead had to pay expensive private health care rates. The estimated cost for recurrent cancer-specific service provision for the Syrian refugee population in Jordan, Turkey, and Lebanon was €3.38M, €26.58M, and €17.72M, respectively, making a total cost €47.67M.

Cancer Services: Provisions and Neglect

Cancer services have been a severely neglected dimension of refugee health, and the global health community must overhaul its perception, vision, and strategy for tackling this issue. The international and global health communities were still caught on the back foot with the massive increase in refugee numbers and the health needs they presented. Initially, this resulted in a very substantial care-gap for NCD refugee health services, which has only begun to be addressed recently. Much of this recent focus has fallen to combating cardiovascular diseases, hypertension, or diseases
with severe and immediate outcomes if treatment is disrupted, such as provision of insulin for type I diabetes or dialysis for kidney disease. However, despite this reprioritization of NCD services, cancer care has received very little attention. Even with the overall NCD category, and despite its substantial burden, cancer represents an acutely neglected dimension of refugee health. Though undoubtedly there are refugees who can access adequate cancer services in particular host-nations, the global picture is disheartening. At the supranational level, the United Nations agencies (WHO, UNHCR) responsible providing leadership for refugee health—which includes identifying priorities and directing the flow of crucial financing—have done little to promote the importance for cancer services.

Cancer in Refugees and Displaced People: Increased Global Response to a Growing Burden

With the growing global burden of cancer and the mass displacement of populations across Asia, Africa, and Europe, we find a particularly neglected community of patients with cancer who, uprooted from their homes, struggle to get access to the services and care they need to manage their conditions. The global health community must overhaul its perception, vision, and strategy for tackling cancer care in refugee populations. There is no predictable end in sight for the drivers of current conflicts, and the incidence of cancer is forecast to rise year after year. The United Nations and nongovernmental organization roles are essential and should be highly supported.

CONCLUSION

Wars, conflicts and natural disasters can cause major disruptions and disruptions for patients already getting treatment for cancer and delays on diagnosis and treatment of displaced people. Patients with cancer are vulnerable to such unexpected circumstances that affect their quality of life, the quality of medical care that they receive, and the available resources and medications that are essential for their treatment. Refugees and displaced people often present with advanced disease. In the Middle East, cancer care for refugees and displaced people is suboptimal because of the limited financial resources and the insufficient national and international support, awareness, education, and access to care. Care of patients with cancer does not fall within high priorities of international relief and humanitarian agencies because of misconceptions that all types of cancers have poor prognosis and that all cancer care is costly. We recommend that patients be treated according to resource-stratified guidelines rather than receive suboptimal or no treatment. Natural disasters and their effect on NCDs, such as cancer, could be avoided by adopting the Sendai Framework for Disaster Risk Reduction by all of the countries that are at risk. This will make the health care systems in these countries more resilient to such unexpected events and will enable them to successfully recover from these disasters in a short period of time with minimal losses. Non-governmental organizations and international relief organizations play important roles in supporting refugees and displaced people, and they should have allocation of more financial resources.

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Global Breast Cancer Research: Moving Forward

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OVERVIEW

Breast cancer is a major global health problem and major cause of mortality. Although mortality trends are declining in high-income countries, trends are increasing in low- and middle-income countries (LMICs). Addressing global breast cancer research is a challenging endeavor, as notable disparities and extremely heterogeneous realities exist in different regions across the world. Basic global cancer health care needs have been addressed by the World Health Organization’s (WHO) proposed list of essential medicines and by resource-stratified guidelines for screening and treatment. However, specific strategies are needed to address disparities in access to health care, particularly access to new therapies. Discussions about global research in breast cancer should take into account the ongoing globalization of clinical trials. Collaboration fostered by well-established research organizations in North America and Europe is essential for the development of infrastructure and human resources in LMICs so that researchers in these countries can begin to address regional questions. Specific challenges that impact the future of global breast cancer research include increasing the availability of trials in LMICs, developing strategies to increase patient participation in clinical trials, and creation of clear guidelines for the development of real-world evidence-based research. The main objective of this review is to encourage the discussion of challenges in global breast cancer research with the hope that collectively we will be able to generate workable proposals to advance the field.

Current projections indicate that the number of new cancer cases is increasing at a fast rate and will evolve from 14 million global cases in 2012 to 22 million by 2030, with the majority of cases occurring in LMICs. There are approximately 1.67 million new cases of breast cancer diagnosed annually, and breast cancer mortality is second only to lung cancer. It is noteworthy that although incidence rates are increasing in most countries, mortality rates are decreasing only in high-income countries, with an estimated 70% of breast cancer deaths occurring in LMICs. Recently reported data from the United States show a 26% decrease in overall cancer mortality over the last 2 decades; breast cancer deaths declined by 39% from 1991 to 2015. Although advances in screening, early detection, and adjuvant treatment are mostly responsible for the decline in mortality in high-income countries, most new cases are recorded in LMICs, where rates of death from breast cancer are increasing.

Although major advances in our understanding of the disease have revolutionized our approach to treatments, guided by the introduction of genomic testing platforms, anti-HER2, aromatase inhibition, and anti-CDK4/6 therapies, substantial challenges remain in the management of some resistant forms of the disease. In the early-stage setting, substantial improvement in breast cancer relapse-free survival rates over the last several decades have been reported, especially in HER2-positive and triple-negative tumors. Results in the metastatic setting, however, leave room for improvement. Recently presented real-world data from France indicate substantial progress in the outcome of patients with metastatic HER2-positive disease, but show no improvement in the 5-year survival of patients with tumors that are HER2-negative, HR-positive and triple-negative.

ADDRESSING BASIC GLOBAL NEEDS

Addressing global breast cancer research needs is challenging, and it is critically important to recognize its heterogeneity around the globe. There are substantial differences in the impact of the disease in different regions. Therefore, although important global questions have been identified, regions may prioritize their needs differently. Although we acknowledge different definitions, in this paper, we consider that the ultimate goal of research is not only to improve the understanding but also the application of how generated data are translated into clinical benefits. We will focus on the most essential areas that require the attention of researchers, and we will briefly review a few fundamental aspects of contemporary global disparities in breast cancer research.

Defining global basic health care needs is always a good place to start. The WHO has proposed a roster of essential medicines for the treatment of cancer, and although important global questions have been identified, regions may prioritize their needs differently. Although we acknowledge different definitions, in this paper, we consider that the ultimate goal of research is not only to improve the understanding but also the application of how generated data are translated into clinical benefits. We will focus on the most essential areas that require the attention of researchers, and we will briefly review a few fundamental aspects of contemporary global disparities in breast cancer research.
Resource-stratified guidelines for the prevention, screening, and treatment of breast cancer have been proposed to address the specific limitations and priorities of LMICs. For example, mammographic screening remains controversial, even though breast cancer is detected at later stages in LMICs, which greatly impacts outcomes compared with high-income countries. Specific recommendations to tackle this very basic and clearly important need are mandatory. Although efforts to address this issue can be identified, practical implementation strategies remain challenging. Research in these areas, although perceived as less important or a lower priority in high-income countries, is vital in most regions of the world.

Finally, access issues are another important global challenge, especially as new and more-expensive treatment alternatives are developed and introduced. Data from the European Federation of Pharmaceutical Industries Association indicate that among the new drugs released into the market in the last 5 years, approximately 90% are used predominantly in three regions: the United States (64.7%), five countries in Western Europe (17.5%), and Japan (7.3%). This leaves about 10% of the consumption for the rest of the world. Although these numbers apply to all pharmaceuticals, it is reasonable to expect there are more pronounced differences in oncology. It is difficult to assess the real impact on outcomes associated with access to new drugs. Nonetheless, it is probably substantial in certain clinical settings, such as the management of advanced HER2-positive disease. Although recognizing and understanding basic global needs for patients with breast cancer is critical, in our view, it is important to include these issues as part of a global research agenda.

**IMPORTANCE OF GLOBAL RESEARCH**

Several of the key aspects addressed here are applicable to many other areas of oncology, and they are all important while considering how to improve global breast cancer research. Collaboration in research efforts is the most important road to the future. Sharing the experience and expertise of research groups and cultures in high-income countries with those in LMICs that have emerging or nearly nonexistent infrastructure is paramount to this process. This is a vital concept that requires global involvement and careful strategic guidance. The ongoing globalization of clinical research, although challenging, is an unavoidable process that should be seen as a major opportunity for the development of research in LMICs. We and others have pointed out the characteristics and particular challenges of the globalization of research, and we project a future with wider distribution of investment, increased qualification of human resources, dissemination of the ability to identify important research questions, and, ultimately, the possibility of conducting regional research focused on local needs.

Worldwide disparities in research infrastructure and human resources must be recognized and provided with specific attention if we want to positively impact global breast cancer research. The financial and logistic requirements of modern trials often exceed available resources in most academic centers. Over the last 40 to 50 years, a considerable percentage—in some cases the majority—of trials and practice-changing research efforts have depended on support from pharmaceutical companies. Independent academic research, although essential to future development, is becoming increasingly difficult to accomplish. If it is to have an objective impact on research scenarios, it needs to be supported with a clearly defined path. Alternative sources of funding are evidently needed and should be actively pursued by governments and societies. This is particularly difficult in LMICs, where medical research and science are in general are low on the list of priorities. On a related note, changing the current societal culture of philanthropy, giving, active participation, and sponsorship of community projects should be the focus of strategic planning as an alternative to industry-supported research. In Latin America, the Latin American Cooperative Oncology Group’s CURA Project is an example of such an initiative.

Addressing the barriers that make clinical trials unavailable in LMICs is also of paramount importance to change practical outcomes. We should recognize that although the intent of drug research is to develop new treatment alternatives, it also represents a partial solution to the access problems in many countries. Though not a definitive solution, availability of clinical research protocols represents a lifesaving alternative for a substantial number of patients with cancer who do not have access to state-of-the-art therapy for their disease. The virtuous circle of clinical research drives the principle that a patient will be treated in the same way, whether she is at the top hospitals in Houston, New York, London, or in any research site in Latin America, Africa, or Asia. The globalization of research we have witnessed over the last few decades represents a clear opportunity to engage the international community in the development of research efforts in LMICs. Similarly, populations of different

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**PRACTICAL APPLICATIONS**

- The ongoing globalization of clinical research, although challenging, should be seen as a major opportunity for the development of research in LMICs.
- Cultural, educational, and socioeconomic characteristics of patients influence enrollment in clinical trials and should be addressed as potential barriers to participation.
- Dissemination of information about ongoing clinical trials to the public is crucial to boost trial participation, facilitate recruitment, and hasten availability of trial results.
- Although particularly challenging in LMICs, independent academic research needs special attention and alternative sources of funding.
- Priorities in breast cancer research vary by region, and, although important global questions have been identified, specific regions might prioritize their own needs.
ethnic backgrounds may respond differently in terms of toxicity and efficacy when submitted to the same treatment, and thus should be studied as part of the drug development process.

CURRENT STATE OF CLINICAL TRIALS IN BREAST CANCER

The analysis of geographic data indicating where clinical research protocols are currently available leads to the identification of the same worldwide disparities observed in other areas. Data from ClinicalTrials.gov show that of the 264,949 clinical trials currently registered, 42% are in North America and 28% are in Europe, whereas only 15.7% are available in Asia and 6.9%, 4%, and 2.5% are available in Latin America, Middle East, and Africa, respectively (Fig. 1). Looking exclusively at the availability of recruiting phase I, II, and III breast cancer trials, of the currently registered 933 studies, only 5%, 3.3%, and 2.5% are available in Latin America, Middle East, and Africa, respectively; all of which are regions where incidence and mortality rates of breast cancer are a progressively major burden (Fig. 2). Additionally, global trials are more likely phase III trials, whereas early phase I and II trials are preferentially performed in North America and Western Europe. Although the discrepancies in trial availability could be better analyzed according to socioeconomic parameters rather than geography, this analysis remains illustrative and challenging.

SELECTED GLOBAL RESEARCH ISSUES AND CHALLENGES

A few selected issues to be addressed to improve global breast cancer research are proposed in Table 1. Although each reader may think other aspects of this complex discussion may deserve inclusion, and probably rightfully so, our main objective here is to promote a debate that will hopefully lead to practical proposals to improve the current state of worldwide cancer research.

Information on and Access to Clinical Trials

Public information about ongoing clinical trials is crucial to boost trial participation, facilitate recruitment, and speed availability of the results. Notably, ClinicalTrials.gov, run by the U.S. National Library of Medicine, was the first online registry for clinical trials and remains the largest and most widely used database. Several other countries have developed similar trial registries. The WHO organized a working group to define best practices for clinical trial registries addressing the minimal and optimal operating standards for trial registration. This international clinical trials registry platform tries to ensure broad access to all those involved in health care.

Although trial registries are an essential part of the global research effort, information on trial locations is not always available or complete, making it difficult for patients and physicians to identify potential studies to join. Improvements in this process are urgently needed to facilitate the practical aspects of patient participation.

An initiative in this direction of speeding up patient enrollment in clinical studies is the INTEGRATE project developed by the Breast International Group (BIG) with the support of the European Commission. This initiative aims to create innovative infrastructures to enable data and knowledge sharing to foster large-scale collaboration in biomedical research. One of the tools of this platform includes an advanced patient screening process for clinical trials, which identifies eligible patients through an automatic evaluation of eligibility by matching patient characteristics to the required criteria of each trial. The platform utilizes patient data available in hospital electronic medical records. Repeated readings of patients’ records can determine their eligibility for multiple trials at different time points in the clinical course. As eligibility determination is challenging and often requires a time-consuming manual chart review, the global application of these platforms could speed up the process of identifying candidates for clinical trials. A similar platform is IBM Watson Health, which generates a ranked list of trials for each patient by relevance and eligibility. Additionally, recent evidence shows that social media can increase clinical trial enrollment and help identify patients with rare tumor subtypes.

In conclusion, development and implementation of technologies through digital platforms, mobile apps, and other social media instruments can have a major impact on access to clinical trials.

Patient Participation in Clinical Research

The substantial progress and success of global research in bringing practice-changing results that are undoubtedly improving outcomes cannot hide the meager proportion of patients who actually participate in clinical trials. The fact remains that a very small minority of patients with breast cancer are enrolled in clinical trials worldwide. Currently, it is estimated that less than 1% of the U.S. population participates in clinical trials, although more than 70% claim they would if recommended by their physician. This rate of participation is likely similar if not poorer in other regions of the world.

This is a particularly challenging subject as we evolve from comprehensive trial design strategies to studies addressing specific tumor subtypes that occasionally represent only a very small percentage of the overall population. Despite being extremely important, this strategy requires a concerted effort to revise and optimize our current complex, very slow, and inefficient drug development process. This issue is further stressed by the fact that minorities and the elderly population, among other subgroups, are consistently under-represented in global clinical trials. Although this discussion is not new, it remains dominant in improving performance and speeding up the development of new treatment alternatives more effectively.

A number of different arguments have a role in this discussion. Most patients consider the option of clinical trials as important to their treatment, and they expect to be informed by their oncologists about such alternatives.
Patients’ motivations for trial participation include potential personal benefit but also the willingness to help others and contribute to scientific research. Recent provocative strategies discuss and propose more direct patient participation in research, leading to a more patient-centric approach. Engagement of patients in some aspects of the design of trials, such as determining the convenience of their participation and gauging their experience during the conduct of the protocol, can indeed improve the process as a whole. Creating patient advisory boards and encouraging advocacy participation will certainly generate suggestions that could optimize enrollment strategies and enhance overall study.
FIGURE 2. Map of All 933 Recruiting Phase I, II, and III Breast Cancer Clinical Trials on ClinicalTrials.gov
designs. On a related subject, making endpoints and trial designs understandable to patients is as important as appropriate and effective communication of the results to the lay public. Listening to patients’ opinions may spawn new ideas and qualify these processes.32

Cultural, educational, and socioeconomic aspects may affect patients’ motivation to participate in studies and can be considered barriers to trial participation, especially in LMICs.15,33-35 Therefore, as illustrated by a recent report from Asia, approaches customized to local and community beliefs are needed to improve trial participation in minority groups of women with breast cancer.36 Importantly, although ethnic background and social disparities do influence the proportion of patients in clinical trials, socioeconomic status does not seem to affect the survival of patients participating in breast cancer clinical trials.37

Strategies to increase the participation of minorities in innovative trial designs and the challenges posed by limited funding availability will require the adoption of effective and efficient recruiting strategies, specialized training, and the active engagement of many stakeholders.38 Patient advocacy groups can partner with researchers and support patients in the process of joining a specific study. Their involvement can assist physicians in reaching out to patients and the public while helping patients make better-informed choices about their care and participation in clinical trials.39 In many countries, cancer advocacy is a new concept, and there is current growth in advocacy activities in many LMICs, particularly in Africa and Latin America.40

Physicians play a critical role in clinical trial recruitment, and their preferences have a considerable impact on the participation of patients. For example, it is well known that oncologists represent a barrier to the inclusion of older patients in breast cancer trials because of the perception that these patients have lower tolerance and higher toxicity.41,42 Consequently, older patients with breast cancer remain mostly under-represented in cooperative group therapeutic trials. A recent study observed some improvement in the accrual of elderly patients to adjuvant trials but a worsening of accrual in neoadjuvant/metastatic trials.43 Therefore, physicians’ involvement and awareness of potential benefits are essential, especially in LMICs where clinical trials are not as frequently available.

Lastly, we must consider the increasing complexity of clinical trials with cumulative requirements for documentation that has led to an escalation in the workload of personnel at clinical trial sites. Therefore, enrolling patients in clinical trials is not only limited by patient issues, but also by physicians’ availability and the infrastructure of the clinical trial sites.44

### Academic Research

Industry-driven studies have tested and registered numerous effective drugs and devices for the diagnosis and treatment of patients with breast cancer. However, academic-led trials should be recognized for the important roles they play in cancer research, especially in studies of new combinations, multimodal treatment regimens, and cost-effective evaluations. Simultaneously, in this era of molecular medicine and immunotherapy, basic and translational research play a crucial role in identifying new anticancer treatments and strategies developed by many academic institutions.

Some important advances in breast cancer are the result of academic-led trials conducted by cooperative groups. For example, the MINDACT trial addressed the safe de-escalation of adjuvant treatment in early-stage breast cancer,45 the HERA trial established trastuzumab as adjuvant treatment in HER2-positive breast cancer,46 and ACOSOG Z0011 showed efficacy in treating patients with sentinel lymph node dissection alone.47

About 35% of trials in Europe are noncommercial, and they are indispensable in the clinical trial landscape.48 To address the lack of awareness on the importance of academic clinical research, the Clinical Academic Cancer Research Forum, a joint initiative by the European Association for Cancer Research, European Organization for the Research and Treatment of Cancer (EORTC), and European Society for Medical Oncology (ESMO), calls on European Union institutions to support this type of research for the benefit of patients.49

Recent data show that the National Cancer Institute’s investment in its cancer cooperative group research program has provided exceptional value and benefit to the American public. On a very telling analysis using data from 23 positive SWOG treatment trials, this study estimated that 3.34 million life-years were gained in the population of U.S. patients with cancer through 2015, at a cost of $125 per life-year gained.50

### TABLE 1. Selected Issues With Practical Implications for Global Breast Cancer Research

<table>
<thead>
<tr>
<th>Issue</th>
<th>Proposed Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access to clinical trials</td>
<td>• Increase availability of trials in low- and middle-income countries</td>
</tr>
<tr>
<td></td>
<td>• Make information on recruiting trials more widely available for patients and physicians</td>
</tr>
<tr>
<td>Patient participation in clinical trials</td>
<td>• Identify and generate specific strategies to counteract limiting cultural, educational, and socioeconomic factors that hinder patient recruitment into clinical trials</td>
</tr>
<tr>
<td>Academic research</td>
<td>• Increase support for all aspects of independent research</td>
</tr>
<tr>
<td></td>
<td>• Develop international collaborations and create innovative infrastructures to enable data and knowledge sharing</td>
</tr>
<tr>
<td>Human resource training</td>
<td>• Stimulate training of qualified personnel, particularly in low- and middle-income countries</td>
</tr>
<tr>
<td>Regulatory issues</td>
<td>• Encourage initiatives of harmonization of regulatory approval processes of clinical trials</td>
</tr>
<tr>
<td>Real-world evidence</td>
<td>• Generate a precise and uniform definition of methods to optimize information collection and minimize bias on real-world data research</td>
</tr>
</tbody>
</table>
Human Resources Training
Building capacity for clinical research in LMICs through international collaboration is an important initiative with far-reaching consequences. We must educate, train, and nurture the next generation of clinical researchers. The Methods in Clinical Cancer Research workshop, jointly organized by the European Cancer Organization, EORTC, American Association for Cancer Research, and ESMO, is one such initiative. Another example is the ASCO International Clinical Trials Workshop (ICTW) that supports cancer research by developing research skills among early-career researchers in LMICs. Early exposure of medical students, oncologists, and other health professionals to clinical research methodology is mandatory to support the development of global research initiatives. Importantly, statisticians focused in cancer research must be trained; they remain a dire need in LMICs.

Regulatory Issues
The launch of a clinical study is time-consuming and influenced by a complex network of multiple oversight bodies with varying objectives and responsibilities. Regulatory timelines are considered one of the most important elements in the conduct of clinical trials. When pharmaceutical companies carry out their category planning, timelines for assessment and approval are considered a key indicator of a country’s attractiveness. Complex and heterogeneous regulations across different geographic and economic regions can hinder the global conduct of studies. For example, an analysis of regional timelines to set up a global phase III clinical trial (ALTTO) of breast cancer showed that upper middle-income countries took longer to obtain regulatory authority approval (median, 123 days) than high-income countries (median, 47 days) and LMICs (median, 57 days). The median time from institutional review board approval to the first recruited patient was 169 days. Therefore, optimizing regulatory processes can boost and facilitate countries’ participation in clinical trials. Accelerating the activation process by removing administrative barriers and nonvalue-adding steps is key to saving precious time in opening clinical trials.

Institutional scientific reviews of clinical trials in oncology contribute substantially to protocol activation timelines. Even though this process is mandatory, optimizing timelines is necessary. The length of review is, in general, associated with the trial phase, timing of approval, and number of committee changes/clarifications requested. The Institute of Medicine and U.S. Food and Drug Administration recognize that activating clinical trials in the United States is lengthy and inefficient. Downstream consequences include increased expenditure, suboptimal accrual, shifting of clinical trials overseas, and delayed availability of treatments for patients. To speed up the process of trial activation, the European Union clinical trial portal and database supports the ambitious modernization of the processes for the authorization and oversight of clinical trials laid down in the EU Clinical Trial Regulation that will come into effect in 2019.

Although worldwide harmonization of good clinical practice standards has been achieved and can be considered a great accomplishment in the development and conduct of clinical research, heterogeneity in regulatory standards is an important issue that has a large impact on the availability not only of trials, but also of newly approved and more effective (and expensive) treatments. Harmonization of trial approval requirements, although conceptually difficult, should remain on our agenda as an important goal.

Need for Real-World Data
Translating clinical research results into clinical practice is another challenge we should tackle. The clinical trial experiment is designed and developed in a controlled fashion with specific inclusion and exclusion criteria. Nonetheless, the confirmation of patient outcomes in a more general population remains an integral part of the process. The generation of what has been called real-world data or evidence is essential to accept the results of a clinical trial as leading to definite benefit in the overall population. The real impact on the whole population is, ultimately, our main objective. This takes on particular importance as we recognize that many of the new additions to our cancer treatments come with benefits that can be statistically significant but have questionable clinical consequences. Both ASCO and ESMO have put forth their proposed criteria to expand the existing criteria far beyond the standard statistical positivity of a trial. Although imperfect, these initiatives help the overall analysis and, as they are discussed, will help regulators and clinicians in the process of incorporating new standards of treatment. Nevertheless, this discussion should be tempered by the fact that we have only rarely evolved with home runs and major changes in cancer treatment. Most of our advances have been incremental, with slow stepwise improvements that have collectively resulted in the major impact on the patient outcomes that we see today.

In this scenario, information obtained outside the constraints of the randomized controlled clinical trial is gaining attention as a potential solution for the frequent lack of generalizability of trial results to specific daily clinical situations. Real-world evidence can be defined as health care information obtained from atypical sources to assess the safety and effectiveness of drugs and devices. Real-world research and the concepts of a planned intervention and randomization in academic scenarios are entirely compatible and will probably be complementary, eventually generating more definitive evidence.

Among other regulatory bodies, the U.S. Food and Drug Administration, has been working on a means to harmonize data collected from nontraditional research platforms to monitor the safety and effectiveness of drugs and medical devices. A precise definition of the appropriate methods to plan real-world research and the specific procedures to collect information are required to minimize bias. Likely, the collection of this evidence will be informative and less
expensive than that of the traditional clinical trial. Recently, ASCO reported that its CancerLinQ network, which includes clinical practices across 40 U.S. states, will share outcome data with the U.S. Food and Drug Administration to inform regulatory decisions. These initiatives carry enormous potential for data generation and the expansion of research opportunities globally.

SETTING RESEARCH PRIORITIES

A number of published efforts have tried to define or prioritize research topics in breast cancer. Although these are all laudable exercises, it is important to understand that priorities do vary in different regions of the world. Furthermore, most of these efforts originate from the perception of unmet medical needs by groups of key opinion leaders and do not necessarily represent the best, unbiased strategy.

Considering these limitations and recognizing that each reader or expert in the field may create a separate list based on personal prejudice, we propose a few topics that may be considered to be priorities within the context of global cancer care (Sidebar 1).

Improving the current clinical trial experiment is mandatory. We must identify barriers that hinder the accelerated inclusion of patients and drug development process. The sooner we obtain results, the quicker we can interpret them and generate new questions that will advance the field. Real-world evidence promises a new perspective with actual, more concrete data on the safety and efficacy of our interventions. At the same time, this area represents an excellent opportunity for global research development, as it will entail much lower costs than the routine clinical trial. The collection of clinical trial data on patients’ postprogression, a related issue, is a straightforward strategy that can help interpreting survival results.

Early detection strategies that are applicable and relevant to LMICs are mandatory and probably more important to study as their direct consequence could be the potentially immediate increase in cure rates. This is particularly attractive considering the reported increasing incidence and mortality rates in these regions. Along the same lines, the identification of patients with genetic predisposition is clearly a key objective as these patients should be offered and subjected to a more-intensive screening program.

Although we have made advances in subtyping the different diseases that comprise breast cancer, we still have a long way to go. An update on the definitions of the criteria for hormone-receptor expression and the consequent different responses we see according to expression levels requires renewed guidelines. Discrepancies in the immunohistochemic and molecular definitions, and the consequences related to outcomes depending on the classification we use, must be clarified. Quick introductions of novel technologies that allow for the detection of circulating tumor DNA and tumor-specific gene alterations will certainly help efforts in subtyping and segmenting our patients and developing new targeted treatment alternatives. These same technologies are assisting with the detection of evolutionary molecular changes that will invariably relate to resistance mechanisms.

Ultimately, we must recognize the fact for far too long we have been treating a large number of patients with early-stage breast cancer who do not require any treatment. Efforts to de-escalate and avoid treatment by selecting only those who will really benefit from adjuvant modalities are mandatory. Another aspect worth mentioning is the fact that we have been unable to define the optimal sequencing of our treatment regimens for patients with advanced-stage disease. Hopefully, the rationale of identifying the specific molecular resistance mechanism will help in developing more sensible and intelligent treatment selection strategies.

CONCLUSION

The unquestionable impact of breast cancer and the ongoing culture of globalization should be seen as opportunities to tackle critical global health priorities, such as the development of research in LMICs, the encouragement of independent academic research, and the improvement of access to clinical trials while increasing patient participation and involvement. Although breast cancer research priorities vary in different socioeconomic scenarios, identification of both global and regional needs is mandatory. Collaboration strategies are essential and should be designed accordingly. At the very least, our objective with this discussion is to attract the attention of established research groups, medical societies, and industry, arguably the major players in defining current and future strategies, to address some of these issues and improve the debate with further deliberations that will hopefully exert a real, positive impact on breast cancer research at a global level.

### Sidebar 1. Selected High-Priority Topics for Global Breast Cancer Research

1. Identify obstacles to improve patient enrollment in clinical trials.
3. Generate criteria for the unbiased design of real-world evidence studies.
5. Define the optimal strategies for mammography/screening, especially in low- and middle-income countries.
6. Develop tools and strategies to identify patients with genetic predisposition.
8. Identify and validate targets of resistance.
10. Define the optimal sequencing of treatments in the advanced-disease setting.
References


Breast Cancer in Latin America: A Map of the Disease in the Region

Eduardo Cazap, MD, PhD, FASCO

OVERVIEW

In the next few decades, breast cancer will become a leading global public health problem as it increases disproportionately in low- and middle-income countries. Disparities are clear when comparisons are made with rates in Europe and the United States, but they also exist between the countries of the region or even within the same country in Latin America. Large cities or urban areas have better access and resource availability than small towns or remote zones. This article presents the status of the disease across 12 years with data obtained through three studies performed in 2006, 2010, and 2013 and based on surveys, reviews of literature, patient organizations, and public databases. The first study provided a general picture of breast cancer control in the region (Latin America); the second compared expert perceptions with medical care standards; and the third was a review of literature and public databases together with surveys of breast cancer experts and patient organizations. We conclude that breast cancer is the most frequent cancer and kills more women than any other cancer; we also suggest that aging is the principal risk factor, which will drive the incidence to epidemic levels as a result of demographic transition in Latin America. The economic burden also is large and can be clearly observed: in countries that today allocate insufficient resources, women go undiagnosed or unsecured for or receive treatment with suboptimal therapies, all of which results in high morbidity and the associated societal costs. The vast inequities in access to health care in countries translates into unequal results in outcomes. National cancer control plans are the fundamental building block to an organized governance, financing, and delivery of health care for breast cancer.

The world is facing a critical health care problem: in the next few decades, cancer will become a leading global public health threat, with rates increasing disproportionately in low- and middle-income countries. Breast cancer is a high priority element of this global cancer threat.1

In the United States, 60% of breast cancer occurrences are diagnosed in the earliest stages; conversely, in Brazil and Mexico, only 20% and 10%, respectively, are diagnosed at an early stage. The all-cancer mortality-to-incidence ratio for Latin America is 0.59, compared with 0.43 for the European Union and 0.35 for the United States. Practically, the risk of dying as a result of breast cancer is double in Latin America than in the United States.2

A study done by our group in 2006, “Breast cancer in Latin America: results of the Latin American and Caribbean Society of Medical Oncology/Breast Cancer Research Foundation expert survey”3 obtained, through a 65-question telephone interview to 100 breast cancer experts from 12 Latin American countries, preliminary information about the state of breast cancer care at that time. The methodology was used to obtain fast qualitative information about breast cancer in the region because of the lack of hard data at that moment.

With respect to epidemiologic characteristics, the incidence of breast cancer in Latin American countries was lower than that in more developed countries, whereas the mortality rate was higher. These differences probably are related to differences in screening strategies and access to treatment. The authors agreed that population-based data were urgently needed to make informed decisions. It was also reported that greater than 90% of countries had, at that time, no national laws or guidelines for mammography screening and that the access rate to mammography was approximately 50%. However, diagnostic testing for hormone receptors and biomarkers were available at most centers (> 80%), and, overall, nearly 80% of patients started treatment within 3 months of diagnosis. In most Latin American health systems, doctors work both at academic institutions and public hospitals, so the subjective interpretation of these data may be inaccurate. Alternative data collection strategies that offer a better understanding of the state of breast cancer care in developing countries could help identify areas for improvement.3

Some of the relevant conclusions of the study are listed in the Sidebar.
A subsequent study published in 2010, entitled “Breast cancer in Latin America: experts perceptions compared with medical care standards,” compared expert perceptions with medical care standards through a systematic review of the norms—recommendations and guidelines considered to be medical care standards (MCS) for breast cancer in 12 Latin American countries. Information related to MCS was requested from government health authorities, cancer institutes, and national scientific and professional societies. The documents received were reviewed by breast cancer experts from each country. In addition, three key survey questions from the 2006 study about early detection and diagnosis were reprocessed to provide information related to the implementation practice of existing MCS. We concluded that all countries included in the study had MCS, whether published by government authorities, national professional or scientific associations, or cancer institutes, or through the adoption of international MCS. The results were reported at the center level (mainly private institutions) or at the country level (public hospitals). Overall, 85% of the experts reported that less than 50% of the women with no symptoms undergo a mammography at the country level compared with 43% at the center level. For diagnostic suspicion of breast cancer, 80% of diagnostic suspicion originated with the patient at a country level compared with 50% screening or medical care at a center. Approximately 30% of patients waited more than 3 months for a diagnosis at the country level compared with 7% at the center level. All of the countries in the study reported the use of similar MCS for breast cancer care. The reported difference between care practiced at a country level versus at a center level suggests that the challenge is not in generating new MCS but in implementing policies and control mechanisms for compliance with existing MCS, which would guarantee their applicability and access to all populations.

### TABLE 1. Relation Between Breast Cancer Incidence and Some Reproductive, Socioeconomic, and Lifestyle Factors From the 2013 Study

<table>
<thead>
<tr>
<th>Country</th>
<th>ASR Incidence Rate (%)</th>
<th>Births in Women Age &lt; 30 Years (%)</th>
<th>Mean Childbearing Age (Years)</th>
<th>Fertility Rate (%)</th>
<th>Overweight and Obesity Rate (%)</th>
<th>Alcohol Consumption (Liters)</th>
<th>Women’s Life Expectancy (Years)</th>
<th>Per Capita GDP in 2008 ($)</th>
<th>Female Education Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uruguay</td>
<td>90.7</td>
<td>64.96</td>
<td>27.7</td>
<td>2.1</td>
<td>73.48</td>
<td>12.7</td>
<td>79.9</td>
<td>8,161</td>
<td>96.3</td>
</tr>
<tr>
<td>Argentina</td>
<td>74.0</td>
<td>65.83</td>
<td>27.9</td>
<td>2.2</td>
<td>77.28</td>
<td>7.6</td>
<td>79.1</td>
<td>9,885</td>
<td>93.3</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>42.9</td>
<td>75.00</td>
<td>26.6</td>
<td>1.9</td>
<td>74.16</td>
<td>7.8</td>
<td>81.3</td>
<td>5,189</td>
<td>74.4</td>
</tr>
<tr>
<td>Venezuela</td>
<td>42.5</td>
<td>75.24</td>
<td>26.8</td>
<td>2.5</td>
<td>74.30</td>
<td>—</td>
<td>76.8</td>
<td>5,884</td>
<td>75.7</td>
</tr>
<tr>
<td>Brazil</td>
<td>42.3</td>
<td>76.58</td>
<td>26.9</td>
<td>1.8</td>
<td>68.40</td>
<td>10.6</td>
<td>76.6</td>
<td>4,448</td>
<td>89.4</td>
</tr>
<tr>
<td>Chile</td>
<td>40.1</td>
<td>65.74</td>
<td>28.0</td>
<td>1.9</td>
<td>76.66</td>
<td>8.2</td>
<td>81.6</td>
<td>6,235</td>
<td>82</td>
</tr>
<tr>
<td>Peru</td>
<td>34.0</td>
<td>63.53</td>
<td>28.5</td>
<td>2.5</td>
<td>78.88</td>
<td>5.6</td>
<td>75.9</td>
<td>2,924</td>
<td>89.9</td>
</tr>
<tr>
<td>Colombia</td>
<td>31.2</td>
<td>72.51</td>
<td>26.5</td>
<td>2.4</td>
<td>70.41</td>
<td>4.7</td>
<td>76.7</td>
<td>2,983</td>
<td>80.9</td>
</tr>
<tr>
<td>Ecuador</td>
<td>30.8</td>
<td>72.25</td>
<td>27.4</td>
<td>2.5</td>
<td>62.75</td>
<td>—</td>
<td>78.1</td>
<td>1,745</td>
<td>—</td>
</tr>
<tr>
<td>Panama</td>
<td>29.2</td>
<td>74.86</td>
<td>26.6</td>
<td>2.5</td>
<td>65.66</td>
<td>—</td>
<td>78.3</td>
<td>5,688</td>
<td>83.5</td>
</tr>
<tr>
<td>Mexico</td>
<td>27.2</td>
<td>71.79</td>
<td>26.8</td>
<td>2.2</td>
<td>79.95</td>
<td>17.3</td>
<td>78.7</td>
<td>7,092</td>
<td>79</td>
</tr>
</tbody>
</table>

Correlation Coefficient: −0.485, 0.378, −0.309, 0.219, 0.112, 0.325, 0.688, 0.679

*p = 0.1306, 0.2519, 0.355, 0.5181, 0.7912, 0.3298, 0.0193, 0.0310

*Estimated overweight and obesity (BMI ≥ 25 kg/m²) prevalence in women age 30 or older in 2005.
**Per capita consumption of pure alcohol by women age 15 and older; drinkers only.
†Combined gross enrollment ratio in education in 2007.
Abbreviations: ASR, age-standardized rate; BMI, body mass index; GDP, gross domestic product.

### PRACTICAL APPLICATIONS

- Breast cancer is the most common cancer in women in Latin America, and, for most cases it is diagnosed at a late stage. Education, awareness, prevention, and early diagnosis are priorities to be considered for all actions performed as part of the breast cancer control continuum.
- Because of the demographic transition, breast cancer rates will approach epidemic proportions with great economic impact. Health systems and physicians must be prepared to face this critical situation.
- Lack of data about the disease is common. It is important to promote better information from reliable data that originates from Latin American countries.
- Access and affordability to proper diagnosis and care are important limiting factors. National general or specific breast cancer plans are fundamental for an organized governance, financing, and health care delivery.
- Evidence-based treatment guidelines are published in most countries by governmental authorities, cancer institutes, or scientific associations. The challenge is the implementation of policies and mechanisms to ensure a consistent compliance with these guidelines across the whole population.
Our study published in 2013, “A review of breast cancer care and outcomes in Latin America,” performed by the Karolinska Institutet, the Stockholm School of Economics, the Pan American Health Organization, the American Cancer Society, and the Latin-American and Caribbean Society of Medical Oncology, analyzed in more detail the picture of the disease according several aspects. Here, we summarize some conclusions about different aspects of breast cancer control determined in this study, which was the last published and most comprehensive one produced by our group.

The study was based on a review of literature and public databases as well as on a survey of clinical experts and patient organizations. The literature review, which focused specifically on treatment patterns and costs of breast cancer in each study country, was conducted in MEDLINE, LILACS, and SciELO but included also gray literature that targeted data and information about the epidemiology of the disease and its outcomes in the region as well as treatment guidelines, cancer control plans, and documentation about the cost of breast cancer.

The study faced a number of limitations, mostly because of the lack of data. Perhaps the most important limitation to bear in mind during interpretation of the results is publication bias. Many factors influence the research and intellectual production in the countries that participated in the study, which resulted in diverse volumes of evidence. Although rich materials and data were identified for some countries, only a few and scattered articles were found for others. Nevertheless, this study is one of the few bodies of comprehensive data available today about breast cancer in Latin America.

EPIDEMIOLOGIC BURDEN
Breast cancer is the most common type of cancer in women in Latin America. Each year, approximately 115,000 women are diagnosed and 37,000 die as a result of breast cancer. Incidence and mortality are increasing: Unlike in Europe or the United States, both incidence and mortality rates are on the rise, and mortality is expected to double in fewer than 20 years. Aging is recognized as the main risk factor for breast cancer; increasing age will cause steep increases in breast cancer occurrences.

Populations in Latin American countries today have relatively low mean ages, but this is bound to change. The demographic profile of Argentina and Uruguay may offer a look into the future of the region: the mean ages there are 5 to 10 years older than the current average, and crude mortality rates as a result of breast cancer are five to six times higher than the current Latin American average. In some countries, including Brazil, breast cancer occurrences are expected to increase quickly and reach epidemic proportions.

According to the available (although limited) comparable data and gathered or constructed series of variables, the only correlations with increased breast cancer risk in Latin American countries are wealth and education (Table 1).

CLINICAL BURDEN
Survival rate in Latin America is considerably lower than the E.U. benchmark, which achieved 5-year survival rates greater than 80%. Enhanced treatments and earlier diagnoses explain progresses made during past years. The available data show a 5-year survival rate in Latin America that fluctuates around 70%, and this difference in survival is caused mainly by the late stage at diagnosis, which is an important predictor for overall survival. Benchmark for detection of early breast cancer in the European Union is 90%, whereas the Latin American average is between 60% and 70%. In countries like Peru, Colombia, or Mexico, approximately 50% of detected breast cancer occurrences are in advanced stages. Late stage at diagnosis negatively affects survival rate and notably increases per-case health expenditures.

SOCIAL AND ECONOMIC BURDEN
The costs of breast cancer are directly related to stage of diagnosis, and annual health care costs for a patient with stage IV breast cancer in Latin America is three to four times the cost of treatment for a patients with stage I disease. The increased morbidity and mortality of patients with metastases greatly increase overall expenses throughout the health care system (e.g., by increasing use of primary care facilities or emergency care while depriving society of productive years).

The ample majority of women are diagnosed when they are still at working ages, so productivity losses as a result of younger age at death are exacerbated by the increased morbidity that results from younger age at diagnosis. Because of insufficient funding, some patients are undiagnosed, untreated, untreated, and uncared for—and others receive suboptimal treatment. General health care expenditure in Latin America is far below European and U.S. standards, not only in absolute but also in relative terms. Annual expenditures per breast cancer occurrence in Europe are approximately $40,000; conversely, in Latin American countries, such as in Brazil for example, values can vary depending on insurance type, from $4,800 in the Sistema Único de Saúde (Brazil’s publicly funded health system) to 16,400 in a private facility.

ACCESS TO TREATMENT AND FRAMEWORK OF CARE
Health care coverage is expanding, although not across all dimensions. Health access in Latin American countries has improved continuously over the years, driven by reforms toward more universal health access and a growing participation of the private sector. Of the three dimensions to universal health access, expansion has been made mainly in terms of the population that is covered. To prevent financial hardship, impoverishment, and social inequity, expansion of the depth of services and proportion of costs covered are critical for catastrophic conditions, such as breast cancer.

Nevertheless, there are vast differences in access to breast cancer care across Latin America that result mainly from insurance type and geographic location. Even within
a particular insurance type or country, great differences in access can exist depending on the wealth of the region (i.e., state or province, municipality) and the willingness to invest in breast cancer care.

As an example, Brazil endows different levels of resources to breast cancer care according to the type of insurance. Inequalities exist on the basis of insurance type. In Argentina, the Compulsory Medical Plan guarantees 100% public coverage for oncology drugs. However, the type and quality of provided treatments vary in different provinces or districts, which causes geographic inequalities. Conversely, in Peru, 64% of the population depends on the public health insurance, which covers breast cancer diagnosis but not treatments. Not surprisingly, health outcomes in Peru are far lower than average and are among the lowest in the region. It is important to mention that this situation has improved in recent years.

Absence of national cancer control programs (NCCPs) contributes to disparities. NCCPs are recommended by the World Health Organization, because they are the blueprint of a holistic cancer control strategy and play a vital role in optimizing health systems and reducing the burden of cancer. The function of an NCCP is to define critical processes in cancer control, such as overall national strategy, priorities, governance, financing, service delivery, monitoring, and continuous improvement. Several Latin American countries do not have formal NCCPs in place, and basic elements of a NCCP, such as population-based cancer registries, are missing or implemented only with a limited scope.

Treatment guidelines exist; the challenge is implementation. Evidence-based treatment guidelines are published in most countries by government authorities, cancer institutes, or scientific associations. The challenge is the implementation of policies and mechanisms to ensure a consistent compliance with these guidelines across the whole population.

**DIAGNOSIS AND TREATMENT**

Generally speaking, there is low commitment to mammography screening. In Latin American countries, most breast cancer occurrences are detected when women seek care after they notice a breast lump. Early detection is an opportunity for improvement in the region, and there is no consistent strategy for breast cancer prevention or detection that could be recognized. Actions are being taken in countries like Mexico, Costa Rica, Argentina, Uruguay, or Brazil, where population-based programs have been or are being implemented.

Hormone receptor and biomarker determination are common practice. Contrary to the low commitment to mammographic screening, post-diagnostic screening with hormone receptor and biologic marker determination seems widespread in the Latin American region. Some questions exist in terms of the differences found in HER2 overexpression, which leads us to conclude (1) that criteria for immunohistochemistry assay interpretation must be standardized and (2) that it is unclear whether HER2 overexpression has been tested consistently.

**SIDEBAR. Conclusions From the 2008 Study on Breast Cancer in Latin America**

- Lack of epidemiologic data
- Lack of political commitment
- Low rate of mammographic screening
- Hormone receptor and molecular markers not available for all patients
- High percentage of mastectomy
- Surgery done by gynecologist or general surgeon in an important number of cases
- Clinical epidemiologic and basic research were insufficient
- Short interval between diagnosis and treatment in some countries
- Adequate palliative care for patients (chemotherapy, hormonotherapy, morphine)
- Good level of education in specialists treating breast cancer

With regard to medical therapy, all systemic treatments are licensed, but budget considerations limit the use of some effective treatments. Adjuvant chemotherapy reduces the relative risk of death each year by almost 40% for women younger than age 50 years and by 20% for women age 50 to 69. Endocrine therapy with tamoxifen in women with estrogen receptor–positive disease results in a more than 30% relative risk reduction of mortality.

One year of adjuvant therapy with trastuzumab in women with HER2-positive breast cancer leads to a 50% reduced risk of recurrence. Use of modern drugs greatly differs from country to country and by insurance type. Chemotherapy treatments with anthracyclines are widely accepted, as is tamoxifen, for patients with estrogen receptor–positive tumors. However, new-generation hormonal treatments like aromatase inhibitors and the biologic therapy trastuzumab are not accessible to all women.

In metastatic breast cancer, medical treatment is the most important consideration. Access to modern drugs is critical but is not a reality. Targeted therapies, such as trastuzumab, bevacizumab, or lapatinib, are important treatment options for patients with advanced breast cancer. Access to these drugs follows restrictions similar to those mentioned for early breast cancer, which leaves patients with few therapeutic alternatives, uncontrolled disease progression, and—consequently—poor outcomes.

**PALLIATIVE CARE**

Quality of life during the end of life is poor in Latin American patients with cancer, and symptoms such as pain, fatigue, nausea, physical impairment, and sleeplessness have been persistent problems. Studies show that care is fragmented; suffering, uncontrolled; and communication among professionals, patients, and families, poor. Also a great burden is placed on patients, families, and caregivers. The main barriers
to optimal pain control are inadequate staff knowledge of pain management (70%), inability to pay for services or analgesics (57%), inadequate pain assessment (52%), and excessive regulations of prescribing opioids (44%)

**BREAST CANCER IN YOUNG WOMEN IN LATIN AMERICA**

Breast cancer among Latin American women is a growing burden throughout the region. The increased proportion of breast cancer occurrences in young women is important, because their diagnoses and tumor behaviors are usually more aggressive than those in their older counterparts. The findings of a recent study reveal that there is scarce information about this matter in Latin American countries, especially about the particular effects and complications that this group of women faces during and after treatment. Also, there are no specific clinical or educational programs that focus on this population. A call to action from health policy planners, medical providers, researchers, patients with breast cancer, families, and the community in general is deserved for better care of this emergent challenge.8

**CONCLUSION**

Breast cancer is the most common cancer, and it kills more women than any other cancer in Latin America. Despite the scarcity of national registries, we corroborated reports of increasing incidence and mortality in most countries. The number of deaths as a result of breast cancer is expected to double by 2030—to 74,000 every year. Aging is the principal risk factor for breast cancer development. Because of the demographic transition in Latin America, breast cancer rates will approach epidemic proportions. Breast cancer burden has different shapes. In Peru, Mexico, Colombia, and Brazil, younger age at diagnosis and at death deprives societies of numerous productive years, as does the high occurrence of the disease in Argentina and Uruguay. The economic burden is also great, and it is clearly observed that countries today allocate insufficient resources to tackle the disease. Women remain undiagnosed, uncared for, or treated with suboptimal therapies, all of which result in high morbidity and the associated societal costs. Universal healthcare coverage is still not the rule in Latin American countries; even in those countries where the entitlement to breast cancer health services are guaranteed by law, it is not accompanied by the necessary resources. Vast inequities in access to breast cancer health in Latin American countries, and even among different regions of countries, exist, which translate to unequal results in breast cancer outcomes. Data about survival are scarce and fragmented; what is available shows a wide dispersion across and also within countries. Yet, the evidence signals that only a few countries have 5-year survival outcomes that surpass 70%. Breast cancer outcomes have improved during the past decade, as evidenced by comparison of the mortality-to-incidence ratios between 2002 and 2008. Costa Rica is the country where most progress is seen, whereas Brazil, Mexico, and Panama have not been able to greatly improve their mortality-to-incidence ratios during the past years. The reduced survival in Latin American countries results in part from diagnosis of approximately 30% to 40% of patients when the disease is already in metastatic phases III and IV; conversely, in Europe, late diagnosis occurs in only 10% of the all diagnoses. Currently in Latin American countries, the majority of breast cancer occurrences are detected when women seek care after onset of symptoms. Initiatives to increase the awareness of breast cancer are important so that women are attentive and do not postpone seeking care until the symptoms have reached a critical stage. No one-approach-suits-all prevention strategy is feasible given the outstanding epidemiologic contrasts in terms of disease occurrence, risks, and available resources both across and within countries. Population-based mammography has been shown to improve outcomes, because it leads to a larger share of breast cancers diagnosed at an early stage; however, in some Latin American countries with limited resources and low incidences, the best screening strategies differ. In countries such as Argentina and Uruguay, versus countries such as Ecuador, Peru, or Mexico, higher frequency, lower starting age, and shorter intervals for screening are justified.

Because affordability remains a limiting factor in the Latin American region, recommendations from the Breast Health Global Initiative and World Health Organization highlight the role of prevention but contemplate several additional measures, such as health education and behavior modification, breast self-awareness, and clinical breast examination. Most Latin American countries have medical care standards; the challenge in this region is to implement policies and control mechanisms to ensure their compliance and applicability to the whole population. NCCPs are the fundamental building blocks to an organized governance, financing, and health care delivery for cancer. There is a marked absence of NCCPs in Latin American countries, which deviates from 2005 World Health Assembly resolutions. Latin American patient groups fulfill an important task when health care systems cannot or do not sufficiently assist patients with breast cancer. Faulty patient information services and lack of government inclusion of these services in policy decision-making should be improved.

**ACKNOWLEDGMENT**

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References


New and Important Changes in the TNM Staging System for Breast Cancer

Gabriel N. Hortobagyi, MD, Stephen B. Edge, MD, and Armando Giuliano, MD

OVERVIEW

Expanded understanding of biologic factors that modulate the clinical course of malignant disease have led to the gradual integration of biomarkers into staging classifications. The American Joint Committee on Cancer (AJCC) TNM staging system is universally used and has largely displaced other staging classifications for most, although not all, cancers. Many of the chapters of the eighth edition of the AJCC TNM staging system integrated biomarkers with anatomic definitions. The Breast Chapter added estrogen receptor (ER) and progesterone receptor (PR) expression, HER2 expression, and/or amplification and histologic grade to the anatomic assessment of tumor size, regional lymph node involvement, and distant metastases (known as TNM). While preserving an anatomic staging system for continuity and for regions where modern biomarkers are not always available, the eighth edition emphasizes the increased prognostic precision of the clinical prognostic stage groups and the pathologic prognostic stage groups. The clinical prognostic stage groups are applicable to all patients with primary breast cancer before any treatment has been implemented, but require a clinical and imaging evaluation as well as a biopsy with grade and available ER, PR, and HER2 results; the pathologic prognostic stage groups are applicable to all patients treated with complete surgical excision as first treatment and also require a complete pathology report, grade, and ER, PR, and HER2. Applying the pathologic prognostic stage groups to a large database of patients staged by basic TNM groupings changed the stage grouping of almost 40% of patients. Grouping by pathologic prognostic stage groups led to a better prognostic distribution of the group and more precise individual prognostication.

Staging classifications were developed to better understand the clinical behavior of specific malignancies, determine prognosis, and enable physicians and their patients to compare outcomes of similar groups of patients. In the early part of the 20th century, multiple staging classifications were developed by experienced clinicians as well as professional organizations. Starting in 1943, and for the next 10 years, Pierre Denoix, a French surgeon, devised a staging system based on the dimensions of the primary tumor, the presence and extent of regional lymph node metastases, and the presence and absence of distant metastases. The system was adopted by the Union Internationale Contre le Cancer (UICC) in 1968, and in 1977, the AJCC published its first staging system based on the TNM concept. Since 1977, the AJCC has developed a detailed and extensive staging system that covers the spectrum of human malignancies and has updated it seven times, as new information about clinical behavior and management strategies has become available. Such updates have been the result of multidisciplinary deliberations by teams of experts, including surgeons, medical and radiation oncologists, pathologists, radiologists, and tumor registry experts, including representatives of the AJCC and UICC. In 1987, with the publication of the fourth edition of the UICC TNM Atlas, the UICC and AJCC TNM classifications were unified. The eighth edition of this staging system, which became effective January 1, 2018, is the most dramatic departure from previous staging classification. In several tumor types, the new staging system has incorporated biomarkers that modify the anatomic TNM classification. Although such changes were incorporated into staging of a few cancers, including prostate, in the past couple of editions, the paucity of appropriately performed analyses of large clinical databases and relevantly formatted results in the peer-reviewed literature precluded the incorporation of most biomarkers into the staging system. In the meantime, the practice of oncology has moved forward, many biomarkers have been incorporated into the process of selecting therapies, especially systemic therapies, and many cancers have been subdivided into specific subtypes based on these biomarkers.

Specifically in the case of breast cancer, it is now considered to be a conglomerate of at least four specific molecular
subtypes based on gene expression profiling: luminal A, luminal B, HER2-enriched, and basal breast cancer. Because gene expression profiling is not available to most practicing physicians, this molecular classification has been adapted to clinical practice on the basis of frequently used biomarker assays: ER, PR, HER2, and some measure of proliferation, usually the Ki-67 assay. As demonstrated by the evolution of classifications in hematologic malignancies (leukemias and lymphomas), it is quite likely several more molecular and clinical subtypes will be identified and validated in the breast cancer field. In addition, multigene assays have been developed, using a variety of technologies, to provide prognostic information for patients with early breast cancer. These assays have also made major inroads into clinical practice and have been validated by retrospective and prospective analyses and, in some cases, by prospective controlled trials. Thus, it became apparent that the AJCC staging system needed to incorporate state-of-the-art biology and prognostic assays or be considered obsolete.

METHODS

In 2013, expert panels were created for each of the major tumor types and charged with developing the best and most effective staging system based on validated prognostic markers and technology that was widely available. The panels were also instructed to keep the anatomic TNM classification as a basic level of staging, so that areas of the world where modern biomarker analyses were not being performed routinely, or at all, could still use the system. The biomarker additions were envisioned as a second tier of prognostication, with genomic assays, if relevant, representing a third layer. The AJCC staff and members of the panels for the seventh edition had kept track of items that users of the staging system had identified as in need of clarification or updating. A list of such items was made available to each panel. In addition, each panel collected peer-reviewed publications that could form the basis for modifications of the staging system. AJCC staff performed a review of the literature, and individual panelists contributed such publications as they thought were relevant to the deliberations of the panel. This paper focuses on the changes that were implemented in the breast staging system. However, considerable changes have also been introduced into the staging systems of many other tumor types.

The major issue under discussion was the integration of biomarkers into the staging system to improve prognostication. Because ER, PR, HER2, and Ki-67 are in widespread use, these were the major focus of the discussion. Histologic and nuclear grade were also discussed in great detail. The panel approached organizations that controlled large, contemporary databases that included information about the biomarkers under consideration and requested analyses to determine the incremental benefit of adding each of the biomarkers, as well as a group of biomarkers, to the basic TNM staging system. These organizations included the National Cancer Database (NCDB), the National Comprehensive Cancer Network, the Early Breast Cancer Trialists’ Collaborative Group, the California Cancer Registry, the National Clinical Trials Network of the National Cancer Institute, and large comprehensive cancer centers. Several of these groups undertook detailed analysis of their databases and provided invaluable information to the panel. The principal source of information was a massive analysis based on 334,243 women diagnosed between 2010 and 2012 and included in the NCDB. Others are still in the process of analyzing their data, and, as the results of such analyses become available, they will be considered in future panel discussions.

The breast panel met by monthly conference calls and had a 2-day face-to-face meeting. All issues raised by previous users and major topics brought up by panel members were addressed and resolved by consensus. The resulting document was placed on a whiteboard under password protection, and all panel members reviewed and made repeated changes. The final document was approved by all panel members and the AJCC executive leadership. Some illustrations from the seventh edition were retained, whereas other new ones were added.

PRACTICAL APPLICATIONS

- Biologic attributes of tumor cells modulate clinical course and therapeutic outcomes.
- Staging systems divide patient cohorts into distinct prognostic categories and allow more precise comparison of patient cohorts, clinical trial results, and therapeutic outcomes.
- ER and PR expressions by breast cancer cells identify different types of breast cancer, with distinct clinical behavior and prognosis.
- Overexpression and amplification of HER2 is associated with adverse prognosis, but it can be overcome with specific anti-HER2 targeted treatments.
- The eighth edition AJCC staging system assumes all patients receive state-of-the-art local, regional, and systemic therapies.
- The use of pathologic prognostic stage groups is the recommended staging system for North America, since it provides more precise individual prognostication.

CHANGES TO THE AJCC/UICC STAGING SYSTEM INCLUDED IN THE EIGHTH EDITION

A number of changes reflected the need to clarify previously included definitions and approaches to specific staging circumstances. Emerging scientific evidence suggested that lobular carcinoma in situ is a benign entity, so it was removed from the list of malignant tumors considered by the Breast Chapter. Standard procedures for defining the dimensions of the primary tumor were addressed: (1) rounding the size of very small tumors was discouraged, (2) T size in the presence of multiple tumor foci was clarified, and (3) a clear definition of satellite tumor nodules in the skin was included.

Clariﬁcations to the N category were also added: (1) measurement of nodal metastases was clearly deﬁned; and (2) cNX was further deﬁned.
The designation pM0 was determined to be invalid, whereas cM1 and pM1 were reaffirmed.

The postneoadjuvant systemic therapy classification was further elaborated: (1) determination of ypT size was clarified to exclude surrounding fibrosis, (2) determination of the dimensions of residual nodal metastases was restated, and (3) the definition of pathologic complete remission was revisited, and clarification was made of pathologic complete remission in the presence of M1 disease.

The major modifications were based on the integration of four biomarkers into the staging system: ER, PR, HER2, and grade (Nottingham Grading System). The panel determined that whenever possible, all invasive cancers should have determination of histologic grade and assays to measure the expression of ER, PR, and HER2, following broadly accepted guidelines, such as those publicized by the ASCO/College of American Pathologists collaboration.9,10 A second tier of prognostication, using information about grade, ER, PR, and HER2, was added to the anatomic information of TN and M: the resulting, combined categories were called prognostic stage groups. Clinical prognostic stage groups were developed for use in all patients with primary breast cancer when all information about anatomic extent and biomarkers is available. The clinical prognostic groups are based on baseline assessment, before any therapeutic intervention has been initiated. It uses clinical assessment of dimensions, based on physical examination and imaging (mammography, ultrasound, and/or MRI). The clinical prognostic stage groups can also be applied to patients who are initially treated with neoadjuvant systemic therapy, chemotherapy, or endocrine therapy; when compared with the baseline clinical prognostic stage, this will provide an accurate assessment of clinical response prior to surgical therapy.

For patients who undergo definitive surgical resection as their initial treatment modality, the new system includes pathologic prognostic staging. This is based on pathologic evaluation of extent of disease (T and N), added to biomarker information. The panel considered this to be the most accurate and precise staging system to be used whenever all of the information was available (Table 1).11 The pathologic prognostic staging should not be used for patients who received neoadjuvant systemic therapy before surgery. Rather, the postneoadjuvant (ypT and ypN) staging system should be used for these patients. Because there are no large enough databases of patients who have received neoadjuvant systemic therapy and have complete information about ypTNM and biomarkers, no prognostic staging system has been developed for this population. The panel will continue to assess the availability of appropriate databases and relevant analyses to develop such a prognostic staging system in the future.

Although the tables associated with these changes in the AJCC staging system are large and complex, it should be relatively easy to find an individual patient’s prognostic stage group by starting from the left of the table and gradually proceeding to the right, using the patient’s specific staging information. In addition, the AJCC is in the process of developing a staging calculator that can be used as a stand-alone application or incorporated into other electronic record and registry systems to further facilitate the determination of an individual’s prognostic stage and, therefore, prognosis.

The addition of biomarkers to the TNM staging system has a major effect on prognostication. It is estimated that upwards of 40% of patients classified by anatomic TNM groupings will change at least one stage grouping when the prognostic stage groups are used.

INTEGRATION OF MULTIGENE PANELS INTO THE STAGING SYSTEM

Over the past couple of decades, and based on the completion of the Human Genome Project, several groups have developed multigene panels that have been shown to provide more accurate individual prognostic information.5,6,12-15 These panels have been used in the determination of prognosis in existing tumor collections, mostly tumor banks, although some used patient samples from prospective clinical trials. These commercially available panels can reproducibly identify patients with better and worse prognosis after initial treatment with curative intent. Most panels were developed for hormone receptor–positive, HER2-negative tumors, although MammaPrint was developed in an unselected group of patients with breast cancer. Most of the clinical validation has taken place in patient groups with lymph node–negative breast cancer, although information based on lymph node–positive breast cancer is starting to appear in the peer-reviewed literature.

MammaPrint was recently tested in a prospective clinical trial (MINDACT) in which risk of recurrence was assessed by MammaPrint and by clinic-pathologic methods (Adjuvant! Online).8 Patients with hormone receptor–positive, HER2-negative, node-negative or -positive, low-risk tumors by both methods were assigned to adjuvant endocrine therapy only; patients with high-risk tumors by both methods were assigned to chemotherapy, whereas patients with discrepant results in the two methods were randomly assigned to use one method or the other to determine whether they should get chemotherapy or endocrine therapy. At the first analysis, MammaPrint identified a group of patients with excellent prognosis who were quite unlikely to benefit from chemotherapy.

The 21-gene assay (Oncotype DX) was the prognostic assay for the TAILORx clinical trial.7 Patients with hormone receptor–positive, HER2-negative, node-negative breast cancer and a recurrence score (RS) lower than 11 were assigned to endocrine therapy alone, whereas those with an RS 25 or higher were assigned to chemotherapy followed by endocrine therapy. Patients with an intermediate RS (11–24) were randomly assigned to endocrine therapy alone or endocrine therapy plus chemotherapy. Only the low-risk group has been reported: these patients had an outstanding result (98.6% disease-free survival at 6.9 years) with endocrine therapy only. The rest of the trial has not been reported. Confirmatory reports from three large databases (Surveillance,
### TABLE 1. Pathologic Prognostic Stage Groups

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<td>Positive</td>
<td>Negative</td>
<td>IIIA</td>
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<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>IIIB</td>
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<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>IIIC</td>
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</table>

Continued
Epidemiology, and End Results (SEER),\textsuperscript{16} West German Study Group PlanB,\textsuperscript{17} and Clalit\textsuperscript{18}) indicate the highly reproducible nature of the assay and provide reassurance that patients with very low RS can safely forego adjuvant chemotherapy.

These two assays have been used in tens of thousands or hundreds of thousands of patients and provide the largest proof of concept that they provide reproducible and reliable individual prognostication. Other assays (PAM50,\textsuperscript{12} Breast Cancer Index,\textsuperscript{13} IHC4,\textsuperscript{14} and EndoPredict\textsuperscript{15}) also identify low- and high-risk populations and could presumably contribute to the biomarker-based prognostic staging system. Based on these results, and on the preponderance of evidence in the peer-reviewed literature, as well as a comprehensive review of the relevant literature by a panel of the ASCO,\textsuperscript{19,20} the AJCC Breast Panel recommended that, when available and indicating a low-risk category, in patients with hormone receptor–positive, HER2-negative invasive breast cancer with a T1-2 primary tumor and negative lymph nodes, these patients should be considered to have a stage IA breast cancer, regardless of the size of the tumor. For the current edition of the AJCC Breast Cancer Staging System, the expert panel applied this change to stage IA only for patients with a low Oncotype DX score. However, the AJCC is committed to more rapid re-evaluation and updating, and it is likely with such updates the panel will include other genomic profiles for this downstaging.

### Table 1. Pathologic Prognostic Stage Groups (Cont’d)

<table>
<thead>
<tr>
<th>When TNM Is...</th>
<th>And Grade Is...</th>
<th>And HER2 Status Is...</th>
<th>And ER Status Is...</th>
<th>And PR Status Is...</th>
<th>Then the Pathologic Prognostic Stage Group Is...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4N0M0, T4N1M0, T4N2M0, T(any)N3M0</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive IIIA</td>
<td>Negative IIIB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive IIIB</td>
<td>Negative IIIB</td>
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<tr>
<td></td>
<td>Negative</td>
<td>Positive</td>
<td>Positive IIIB</td>
<td>Negative IIIB</td>
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<td>Negative</td>
<td>Negative</td>
<td>Negative IIIB</td>
<td>Negative IIIB</td>
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<td>IIIB</td>
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<td>IIIB</td>
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<td>Positive</td>
<td>IIIB</td>
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<td>IIIB</td>
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<td>Positive</td>
<td>IIIC</td>
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<td>Negative</td>
<td>Positive</td>
<td>IIIC</td>
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<td>Negative</td>
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<td>Positive</td>
<td>IIIC</td>
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<td></td>
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<td>IIIC</td>
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<td>Negative</td>
<td>IIIC</td>
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<tr>
<td></td>
<td>Positive</td>
<td>Positive</td>
<td>IV</td>
<td></td>
<td></td>
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<tr>
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<td>IV</td>
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<td></td>
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<tr>
<td></td>
<td>Negative</td>
<td>Negative</td>
<td>IV</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Includes T1mi.

**Does not include N1mi.

For cases in which HER2 is determined to be equivocal by in situ hybridization (ISH; fluorescence ISH or chromogenic ISH) testing under the 2013 ASCO/College of American Pathologists HER2 testing guidelines, the HER2-negative category should be used for staging in the pathologic prognostic stage group table. The prognostic value of these prognostic stage groups is based on populations of persons with breast cancer who have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy).

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Abbreviations: TNM, tumor node metastasis; ER, estrogen receptor; PR, progesterone receptor.

### Use of Prognostic Scores

Another approach, perhaps somewhat simpler, to determine individual prognosis is based on information obtained from multivariable analysis of a large database housed at
NEW AND IMPORTANT CHANGES IN THE TNM SYSTEM

The University of Texas MD Anderson Cancer Center in Houston, TX, which is an NCI-Designated Cancer Center. The institution developed an online, prospective database of all patients with breast cancer treated or assessed at the institution since 1997. The database provides detailed information about patient demographics, tumor characteristics, treatment modalities used, and outcomes. Information in the database is updated about once a year. Investigators identified 3,728 patients treated with definitive surgery and appropriate adjuvant treatments between 1997 and 2006 and with complete biomarker information. Univariate and multivariate analyses were performed to identify factors associated with disease-specific survival (DSS). Variables associated with outcomes were assigned points, and a prognostic model based on the sum of points was developed (Table 2). Development on the MD Anderson Cancer Center database (Table 3), the prognostic score was validated on a cohort of patients of the SEER database and subsequently on the California Cancer Registry database (Table 4).

CLINICAL RELEVANCE OF CHANGES TO THE AJCC STAGING SYSTEM

A few clinical examples might illustrate the impact of these changes on clinical practice.

- A 58-year-old schoolteacher developed a lump in the right breast. By physical examination, it measured 3.5 × 4.0 cm. By imaging, the lesion measured 3.2 × 3.6 cm. There was no palpable axillary lymphadenopathy. A percutaneous needle biopsy showed a grade 2 invasive ductal carcinoma (IDC), ER+, PR−, HER2−. The patient underwent breast-conserving surgery, which confirmed an IDC, measuring 3.0 × 3.5 cm. Sentinel lymph node biopsy was negative. An Oncotype DX assay was requested and showed an RS of 9. Using the basic TNM staging system, the anatomic stage for this primary breast cancer would be IIA (pT2N0M0). Applying the new clinical prognostic stage groupings would also lead to a stage IIA. The pathologic prognostic stage would be IIA, and, with the result of the Oncotype DX RS (genomic modifier), her tumor would be downstaged to IA.

- A 63-year-old homemaker developed a lump in the left breast. By physical examination, it measured 7.5 × 6.0 cm. By imaging, the lesion measured 8.2 × 6.6 cm.

TABLE 2. Univariate and Multivariate Analysis of Prognostic Factors in Relation to Disease-Specific Survival

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>5-Year DSS (%)</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>p</td>
<td>HR</td>
</tr>
<tr>
<td>Pathologic stage (seventh edition)</td>
<td></td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>I</td>
<td>99.1</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>IIA</td>
<td>98.0</td>
<td>2.8</td>
<td>.002</td>
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<tr>
<td>IIB</td>
<td>95.6</td>
<td>4.8</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>IIIC</td>
<td>95.4</td>
<td>6.8</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>III</td>
<td>79.5</td>
<td>26.6</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Nuclear grade</td>
<td></td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>I</td>
<td>99.8</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>II</td>
<td>98.9</td>
<td>5.0</td>
<td>.1</td>
</tr>
<tr>
<td>III</td>
<td>95.3</td>
<td>25.0</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td>Referent</td>
</tr>
<tr>
<td>Positive</td>
<td>98.8</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Negative</td>
<td>92.9</td>
<td>4.9</td>
<td>&lt; .0001</td>
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<tr>
<td>PgR status</td>
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<td>Positive</td>
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<td>Referent</td>
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<td>95.2</td>
<td>4.0</td>
<td>&lt; .0001</td>
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<td>HER2 status</td>
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<td>Referent</td>
</tr>
<tr>
<td>Positive</td>
<td>97.5</td>
<td>Referent</td>
<td>Referent</td>
</tr>
<tr>
<td>Negative</td>
<td>98.0</td>
<td>0.8</td>
<td>.5</td>
</tr>
</tbody>
</table>

Abbreviation: DSS, disease-specific survival; ER, estrogen receptor; PgR, progesterone receptor. Reprinted with permission from Amin et al.3

TABLE 3. Determination of Risk Score/Profile

<table>
<thead>
<tr>
<th>Factor</th>
<th>0 Points</th>
<th>1 Point</th>
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</thead>
<tbody>
<tr>
<td>Grade 1/2</td>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>ER status</td>
<td>ER-positive</td>
<td>ER-negative</td>
</tr>
<tr>
<td>HER2 status</td>
<td>HER2-positive</td>
<td>HER2-negative</td>
</tr>
</tbody>
</table>

Abbreviation: ER, estrogen receptor.
There was one palpable axillary node measuring 1.5 × 1.5 cm. Biopsy showed a grade 1 IDC, ER+, PR+, HER2+. Breast-conserving surgery confirmed an IDC measuring 8.0 × 6.5 cm. Sentinel lymph node biopsy was positive.

The anatomic stage of this tumor would be IIIA (pT3N1M0), the clinical prognostic stage IIA, and the pathologic prognostic stage IB. Note, however, that the change in prognosis is based on the assumption that if it is appropriate in her personal circumstance, she is offered and receives systemic therapy based on the T, N, and biomarker status of her cancer.

- A 72-year-old executive was found to have a mammographic abnormality in the right breast. The lesion was not detectable by physical examination. By imaging, the lesion measured 1.1 × 0.8 cm. There was no palpable axillary node. Biopsy showed a grade 3 IDC, ER−, PR−, HER2−. Breast-conserving surgery confirmed an IDC measuring 8.0 × 6.5 cm. Sentinel lymph node biopsy was positive (0.4 cm). Axillary lymph node dissection not performed. Oncotype DX RS was not performed (not indicated for triple-negative breast cancer).

Anatomic stage: IIA (pT1N1M0); clinical prognostic stage: IB; and pathologic prognostic stage: IIA.

- If this 72-year-old executive had been diagnosed with the exact same cancer but different biomarker profile, ER+, PR+, HER2+, her anatomic stage would still be IIA (pT1N1M0), but her clinical prognostic stage would be IA, and her pathologic prognostic stage would be IA. This would again have major implications on the selection of optimal adjuvant therapy.

**CONCLUSION**

The development of these prognostic models was a major step forward for the AJCC staging system. However, it is understood that this system will require ongoing revision as information on biomarkers, genomic profiles, and treatment evolves. The AJCC is committed to making such revisions more often than the historical 6- to 8-year revision cycle. The NCDB represents a very large group of patients, but, when distributed into 120 possible stage groups, the numbers decrease dramatically. In addition, the median follow-up of this large cohort was only 41.7 months. Although this provides a reliable preliminary analysis, longer follow-up will be needed, in view of the rather protracted nature of some breast cancer subtypes. This is particularly true for hormone receptor–positive breast cancers, for which a 10-year follow-up is barely acceptable, and recurrences continue to occur for more than 20 years. Unfortunately, the collection of information about hormone receptors and HER2 did not start in earnest until 2010 in the SEER database and the NCDB. Larger databases of patients treated with state-of-the-art therapies, longer follow-up times, and confirmatory analyses from other large oncology databases will help refine the modifications implemented in the eighth edition.
edition of the AJCC staging system. Something similar must be said about the multigene panels and their role in staging. Although the databases of patients whose tumors have been tested with these assays is growing, the denominator is usually much smaller when, in addition to the results of genomic assays, complete clinic-pathologic information, biomarkers, and appropriate follow-up with outcomes is sought. The development of more sophisticated multigene panels in triple-negative and HER2-enriched populations would be a welcome addition in the future. We have taken the first steps in biology-driven staging and prognostication in breast cancer. As our knowledge base expands and the use of personalized cancer therapy grows, our staging systems will continue to improve.

References


GYNECOLOGIC CANCER
Care After Chemotherapy: Peripheral Neuropathy, Cannabis for Symptom Control, and Mindfulness

Deanna Teoh, MD, Thomas J. Smith, MD, Mihae Song, MD, and Nick M. Spirtos, MD

OVERVIEW

As cancer therapies improve, patients are living longer. With these improvements in therapy comes a responsibility to optimize patients’ quality of life during cancer therapy and beyond. This report reviews three timely and important topics. The first section reviews the mechanism underlying chemotherapy-induced peripheral neuropathy and evaluates the evidence for interventions to prevent and treat peripheral neuropathy. It also provides a framework for approaching the diagnosis and management of this common and bothersome side effect. The second section addresses the controversial but effective use of cannabinoids for cancer and chemotherapy symptoms. Although clinical trials are difficult to conduct because of the political and social stigma of this class of drugs, this review provides evidence of the efficacy of cannabinoids for treatment of pain and nausea. The last section addresses the mind-body connection, with a focus on the negative emotions patients with cancer often experience. This section assesses the literature regarding mindfulness-based programs to improve cancer-related stress. These three topics may appear unrelated, but all address one common goal: treating the body and the mind to optimize quality of life during and after cancer therapy.

Quantity of life for many cancer patients is improving steadily; now we need to do the same for quality of life. — Peter Cardy, Chief Executive, Macmillan Cancer Support

Most patients with cancer cannot wait to complete their treatment. But healing is not complete when treatment stops. Many patients have lingering physical side effects from their cancer or their treatment, including but not limited to pain, neuropathy, fatigue, physical weakness, sexual dysfunction, and altered body image. Most patients also have strong emotions associated with their cancer diagnosis and treatment, and this can further augment the physical side effects. This review provides an introduction to treatment of some of these long-term effects, including prevention and management of chemotherapy-induced peripheral neuropathy, the medicinal effects of cannabis and the social and political context of this therapy, and the effects of mindfulness-based therapies.

PREVENTION AND TREATMENT OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

Your Patient Has Chemotherapy-Induced Peripheral Neuropathy. Now What?

As a breast oncologist, one of my biggest concerns is the damage that the drugs I have administered have caused to an ever-increasing number of survivors. We review what we have learned from medical oncology, palliative medicine, and neuromodulation about chemotherapy-induced peripheral neuropathy (CIPN). The only thing good thing to say about CIPN is that it indicates maximal tolerance of the organism and might be good for outcomes; median overall survival of patients with pancreatic cancer in a nab-paclitaxel trial who developed grade III versus grade 0 CIPN was 15 months compared 6 months (HR 0.33; p < .0001). First, take CIPN seriously. It occurs in 30% to 40% of people receiving platinum, taxanes, proteosome inhibitors, and an ever-increasing number of drugs. Sensory neuropathy may be worse in black or African-American women. Only recently have we recognized the phenomena of “coasting,” wherein the damage may continue for months after the treatment ends, especially after treatment with oxaliplatin or cisplatin. CIPN has long-standing consequences, with 47% of people reporting significant bothersome symptoms 6 years after treatment. Of those with CIPN, the fall risk is increased by a hazard ratio of 1.8. Second, routinely ask about CIPN because CIPN is relatively easy to diagnose. Ask, “Are you having any pain, numbness, or tingling since you started chemotherapy?”, “Have you had any falls?”, and “Is the CIPN bothering you enough that we should treat it?” Third, we can be cautiously optimistic that the future will be better as we understand the basic science of CIPN. To date, ASCO can only recommend duloxetine for treatment, and nothing at all for prevention. However, that is slowly changing. The main damage causing CIPN appears to be to the mitochondria in
the cell body at the dorsal horn, with inability to repair the terminal arborization of the longest nerve fibers—hence the damage to the longest nerves first. Other targets include rare inflammatory neuropathies in the brain and spinal cord from PD-1 and CTLA-4 inhibitors. There are also rare reports of delayed bowel obstruction from oxaliplatin.

**What Helps to Prevent CIPN?**

Table 1 lists established and potential ways to prevent CIPN. Right now, only exercise prevents CIPN, and although the effect size is measurable, it is small. The data come from a secondary analysis of a randomized trial of exercise to prevent fatigue and do show reductions of 0.3 (on a scale of 0–10) in numbness/tingling and 0.4 in hot/cold sensations. Missing from the data is the effect on pain, which was not measured. Regardless, exercise has so many good attributes it should be a standard prescription for all patients.

Drugs to prevent CIPN are finally appearing. Calmangafo-dipir, which mimics manganese superoxide dismutase and protects mitochondria from oxidative stress, was somewhat effective in a randomized phase II trial, reducing sensory CIPN symptoms and reducing the risk for grade 2 or higher CIPN (HR 0.62). Side effects were minimal, and the anticancer efficacy of leucovorin/fluorouracil/oxaliplatin (FOLFOX) therapy was unchanged.

Wrapping the extremities in cold also appears to prevent some parts of CIPN. As an example, in women treated with paclitaxel who underwent regional cooling (think cold socks and gloves) the incidence of grade 2 or higher CIPN was 5% to 9% versus 20% to 32% in comparison groups. Randomized trials are ongoing. Of course, that will not work with oxaliplatin.

**PRACTICAL APPLICATIONS**

- **As our patients live longer, it is paramount that we seek ways to optimize quality of life through management of common side effects, such as chemotherapy-induced peripheral neuropathy, use of emerging and effective therapies, and recognizing the mind-body connection and integrating mindfulness-based programs with standard therapy.**
- **Peripheral neuropathy is a common side effect of multiple cancer therapies but may be minimized or prevented by exercise, cold wraps, and emerging drugs that protect the mitochondria.**
- **Drugs such as duloxetine, opioids, certain anticonvulsants, and menthol, as well as newer therapies such as neuromodulation, may treat existing chemotherapy-induced peripheral neuropathy.**
- **Although commercially available dronabinol is not superior to other antiemetics and oromucosal nabiximols is not very effective for treating cancer pain, cannabis has been shown to be effective for treating pain and may help patients reduce opioid intake.**
- **Mindfulness-based programs have been shown to decrease stress and anxiety in patients with cancer and to decrease cortisol and cytokine levels associated with stress.**

**What Treatments Help Established CIPN?**

Treatments do exist for existing CIPN (Table 2). Folklore that opioids do not work in neuropathic pain is common. However, the data show that compared with placebo, opioids control neuropathic pain as well as they do other types of pain, but the number needed to treat, approximately three, is about the same as with other neuropathic pain drugs.

First, start with duloxetine. It is the only drug proven to work in randomized controlled trials. Do not start with gabapentin or pregabalin. If duloxetine does not work, or the effect is not sufficient or side effects too large, then switch to an alternative drug. This will require 3- to 4-week trials until something works, or the CIPN remits, or you just get tired of trying. But refer to an interested neurologist, pain manager, or palliative care specialist rather than just give up. It takes patience to do sequential 4-week trials.

Second, continue the opioids. Add drugs proven to work along with opioids, such as nortriptyline, starting at 10 mg at night and increasing up to 100 mg, or gabapentin, 300 mg at night with a target dose of 1,800 mg per day. In other types of neuropathic pain, nortriptyline and gabapentin have demonstrated a synergistic effect, potentially allowing avoidance of opioids. If no other drugs have helped, switch the drug class to carbamazepine or oxcarbazepine to quiet damaged nerve impulse generation.

Third, add nontoxic treatments. Fallon and colleagues’ proof-of-concept trial showed that 1% menthol (think “back rub” in the local drugstore or lotions with menthol used to treat skin ailments) did not help pain scores due to CIPN, but people did report improvements in walking, sleep, and catastrophizing (“nothing will ever get better”). Additionally, 81% of patients reported improvement in neuropathy symptoms, often substantial. Although this will not work for everyone, it is incredibly easy, inexpensive, and very patient-centered. Instruct your patients to apply this treatment to the affected areas and the low back (where the nerves from the leg would enter the spinal cord) twice a day for at least a month. The principle is that the menthol binds to surface receptors, sends a cooling message along the native nervous system, and may reset the local nerves or the pain areas of the brain.

Finally, think out of the box about neuromodulation. We found at least a dozen successful cases and no failures with spinal cord stimulation, but this technique is invasive and expensive. Pachman and colleagues reported a positive result from Scrambler (Calmare Therapeutics Inc., Rutherford, NJ) therapy, which uses surface electrodes to capture the surface receptors of the c-fibers (which carry pain impulses) and send a “nonpain” impulse along the usual route to the brain. Treatment duration is approximately 45 minutes daily until the pain is relieved. Results were better than with duloxetine. Our own group reported little effect in a sham-controlled Scrambler therapy trial, but because we have changed our technique to completely avoid any
dermatomes that have altered sensation, we have had multiple consecutive successes (unpublished data submitted for presentation at the 2018 ASCO Annual Meeting).

**Take-Home Messages**

First, ask about CIPN symptoms. Second, be prepared to do multiple 3- to 4-week trials of duloxetine first, then pregabalin or gabapentin, then nortriptyline, and keep going. Refer to a pain manager, neurologist, or palliative care specialist if you do not have the experience or patience. Watch for new information about mitochondrial protection agents; cold-prevention gloves and socks; treatment with topical agents, such as 1% menthol, to bind surface receptors for damaged nerves; and treatment with superficial neuromodulation, such as Scrambler therapy.

**MEDICINAL EFFECTS OF CANNABIS**

**Cannabis Politics**

Over the last 150 years, the perceived and reported medicinal effects or benefits associated with the consumption of products derived from the cannabis plant have fluctuated as much as the most volatile stock market period in history. Periodically, the benefits have been held out to be Olympian in nature, almost a cure-all for all conditions, whereas at other times use of cannabis has been associated with “reefer madness,” including suicidal ideation, sexual promiscuity, and in general uncontrolled impulses. The truth, as usual, lies somewhere in between. Add in a dose of world politics and posturing, difficulty in conducting cannabis trials, an error in taxonomy, the radically different effect ascribed to the two main components of the plant, delta-9 tetrahydrocannabinol and cannabinol...
(THC) and cannabidiol (CBD) consumed in a variety of ways, a less than clear understanding of the metabolism of the compounds and the endocannabinoid system, and the inability to link a specific plant profile to a specific outcome, and it becomes even more difficult separating the flower from the trim, as it pertains to cannabis sativa and its medicinal effects.

For the purposes of this forum, the historic marketing of cannabis and its byproducts will be left to an excellent reference, as will references to reefer madness-type publications. Regarding world and U.S. politics, our present-day situation, for the most part, is still governed nationally by the Nixon administration ignoring the recommendations of the National Commission on Marihuana and Drug Abuse (The Schafer Commission) and its appendix, both published in 1972, which called for decriminalization of personal possession and use of cannabis. Even this report was not without controversy. To paraphrase a report issued by the Committee on Public Health of the New York Academy of Medicine, it recommended that a government agency investigate the feasibility of control and distribution of marijuana through a government agency, whereas a New England Journal of Medicine editorial suggested that legalization offered the best promise for effective control of marijuana. Nahas and Greenwood published a detailed rebuttal to the Shafer Commission report and ultimately the administration ignored the Commission’s recommendations. Currently 28 states, the District of Columbia, and a few of the more than 500 recognized native tribal nations have passed laws regulating the sale of cannabis for medical or for both medical and recreational use, and the laws enacted by each of these governments or their legislation are at odds with federal statute. The recent rescinding of the Cole memorandum by U.S. Attorney General Jeff Sessions has added fuel to the fires of confusion, which unfortunately will not be solved here. All should be left with the warning of “buyer beware.”

| TABLE 2. Interventions Used to Treat Chemotherapy-Induced Peripheral Neuropathy |
|--------------------------------|----------------|----------------|----------------------------|
| **Intervention**             | **Effect Size** | **Practicality** | **Comment**                |
| Effective                    |                |                |                            |
| Duloxetine                   | Effect size, 0.513 (p = .003); mean difference in pain scores was 0.73, so about a point | Administer just as in the trial: start at 30 mg for a week, then increase to 60 mg | Effect was seen within 1 month, so if there is no benefit or if side effects occur, stop and try something else |
|                               |                |                |                            |
| Exercise                     | Total CIPN symptoms: approximately 0.5/10 difference | Exercise for Cancer Patients (EXCAP): individually tailored daily moderately intense walking, therapeutic band exercises (e.g., squat, side bend); both increased over 6 weeks |
|                               | Numbness and tingling: 0.20 effect | Not readily available | Visual and auditory rewards were given for voluntary changes in EEG; not placebo controlled |
| Neurobiofeedback             | On Brief Pain Inventory, “worst” pain reduced by 2.4, clinically significant (p = .001) | Not readily available | Visual and auditory rewards were given for voluntary changes in EEG; not placebo controlled |
| Scrambler therapy            | Effect size similar to or exceeds that seen with duloxetine | Not readily available but safe |
| Topical 1% menthol            | 81% of patients reported improvement with no harm | Readily available | Not placebo controlled, but no harm |
| Spinal cord stimulation       | Few published cases but can be effective | Trial determines whether there is any benefit before implantation | Readily available at most pain centers |
| Ineffective in RCT but commonly used: | | | |
| Gabapentin                   | 44% taxanes, 20% platinums, 27% combinations — no effect | 44% taxanes, 20% platinums, 27% combinations — no effect |
|                              | We have all had patients who get worse when gabapentin is stopped, so there are some responders. Just use as second line and in combination. |
| Pregabalin                   | Not adequately tested | No a priori reason to suspect this is better than gabapentin, but it could be better tolerated |
| Reflexology                  | No difference in CIPN severity or incidence; slight improvement in sensory symptoms | Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; EEG, electroencephalography; RCT, randomized clinical trial.
The Science Behind Medicinal Cannabis

As with staging systems for each cancer, we can all argue the merits of the specifics defining each stage, but none would argue against the need for uniformity. For without it, discussion of results and therefore evaluation of new treatments would be rendered impossible. *Cannabis* was taxonomically divided into three species in the 1970s: *C. indica*, *C. sativa*, and *C. ruderalis*. Adding to the confusion, yet ultimately clarifying, was the work of McPartland, who proved on a genetic basis that these were all the same species, just different subspecies.38 More importantly, he found that *C. sativa* originated in India and should have been classified as *C. indica*, *C. indica* originated in Afghanistan and should have been identified as *C. afghanica*, and *C. ruderalis* is most properly classified as *C. sativa*. Until this nomenclature is standardized, comparing research results will be near impossible.

Since Mechoulam’s group identified and synthesized both CBD and THC, the psychoactive component in the cannabis plant, more than 60 phytocannabinoids have been identified in addition to approximately 400 other components of the cannabis plant. These include many terpenes that account for the associated aroma and that may contribute to the entourage effects of cannabis.39,40 Research efforts have logically been based on our understanding of metabolism via the cytochrome P450 pathways and the cannabinoid receptors currently identified throughout the body, particularly in the brain. Left to further study is the molecular basis for the therapeutic effect of associated with CBD, as it has little affinity for the CB1 and CB2 receptors.41-43 Of most importance at this time has been the identification of CBD acting as a negative allosteric modulator, thereby changing the shape of the CB1 receptor and dampening the psychoactive effect associated with the consumption of THC when taken in combination with CBD.44

Medicinal Effects of Cannabinoids

Much of our collective knowledge regarding the clinical effects of cannabinoids comes from case reports and retrospective observational studies. Few prospective randomized clinical trials have been reported. Russo has provided an excellent review of controversies associated with research in this area, including issues involving clinical trial approval and design.45 Russo highlighted the difficulties encountered in attempts to conduct research involving cannabis, in particular the need to use cannabis provided exclusively by the University of Mississippi or to apply to cultivate and supply the study drug. Of note, although the U.S. Drug Enforcement Administration and the U.S. Food and Drug Administration make it challenging to obtain cannabis to conduct medical research, the U.S. Patent and Trademark Office has issued a wide range of patents involving cannabis: for its cultivation, methods for extraction and manufacturing, and products combined with any of several other compound proven beneficial in the treatment of certain medical conditions. Predictive Therapeutics LLC (Salt Lake City, UT) was issued U.S. Patent 9,149,499 B1 on October 6, 2015, for the combination of cannabis and any nonsteroidal anti-inflammatory drug and any progestin with the intent to treat pelvic pain and/or endometriosis. Others, including the U.S. government, have been issued patents for cannabis-related products (Table 3).

On one hand, conducting studies necessary for such applications is made difficult at best; however, those intending to commercialize cannabis-based therapies have been given the green light. In Nevada specifically, efforts to conduct federally approved research with the intent of filing a new drug application have been thwarted as the institutional review board at the university medical center requires Drug Enforcement Administration assurance before considering any protocol containing cannabis in a treatment arm, yet to obtain federal permission one needs institutional review board approval for study of the drug of concern.

Given these difficulties conducting cannabinoid research, many studies that pertain to clinical oncology involve the use of dronabinol to relieve chemotherapy-induced nausea and vomiting and pain. May and Glode have thoroughly reviewed much of this literature.46 Dronabinol has offered little relief over other available antiemetics. Additional prospective studies have using oromucosal nabiximols (THC:CBD ratio of 1:1) for intractable spasticity in patients with multiple sclerosis led to the U.S. Food and Drug Administration granting GW Pharmaceuticals (London, United Kingdom; Carlsbad, CA) approval for this indication.47,48 A randomized clinical trial using the same product to treat cancer-associated pain showed oromucosal nabiximols to be no better than placebo.49 Maccarone and colleagues have reviewed results of trials involving oromucosal nabiximols and concluded they were both tolerated and efficacious.50

Addressing the opiate crisis in this country has led to many studies being conducted using cannabis-based therapy as an alternative means of managing chronic and cancer-related pain. Although nabiximols are not statistically superior to placebo for controlling pain in patients with cancer, other randomized placebo-controlled trials have demonstrated the efficacy of using cannabis for pain control.51-53 Evidence also suggests that a cannabis-opioid interaction exists, resulting in improved pain control.54 All the studies to date have used pain scales or patient interview results to determine the success or failure of the cannabis intervention. Given the increasing availability of legal cannabis, there will be fewer opportunities to study a cannabis-naïve population—it is clear from the work of Bachhuber and colleagues that patients are self-treating with cannabis to reduce if not eliminate their dependence on narcotics. This is reflected by the 24% reduction in opiate-related deaths in states with legalized medical marijuana programs as compared with those without.55

We, a group of physicians in Nevada, are licensed to cultivate, produce, and sell cannabis-related products. We have previously conducted a single-arm pilot study enrolling 25 patients with a history of at least 3 years of long-term opiate use, with a study endpoint of decreasing opiate intake, as determined by weekly pill count, by 30%. Results from that study exceeded our goal, with a decrease in opiate intake by greater than 50% in 92% of patients (N. Spiratos, manuscript...
in preparation). This provides an objective basis from which to evaluate the potential of cannabis to reduce opiate consumption across the United States. We are conducting a randomized, placebo-controlled study using a guava-based syrup with a THC:CBD ratio of 2:1 and a placebo containing only the guava-based syrup. We have also opened a trial to evaluate the effectiveness of this syrup with some slight modifications in the terpene profile to control chemotherapy-induced nausea and vomiting. These results will be presented at the meeting.

### TABLE 3. Cannabis Patents

<table>
<thead>
<tr>
<th>Cited Patent</th>
<th>Filing Date</th>
<th>Publication Date</th>
<th>Applicant</th>
<th>Title</th>
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<tr>
<td>US4279824</td>
<td>November 1, 1979</td>
<td>July 21, 1981</td>
<td>Laurence O. McKinney</td>
<td>Method and apparatus for processing herbaceous plant materials, including the plant cannabis</td>
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<tr>
<td>US6403126</td>
<td>January 24, 2000</td>
<td>June 11, 2002</td>
<td>Websar Innovations Inc.</td>
<td>Cannabinoid extraction method</td>
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<tr>
<td>US6630507</td>
<td>April 21, 1999</td>
<td>October 7, 2003</td>
<td>United States of America as represented by the Department of Health and Human Services</td>
<td>Cannabinoids as antioxidants and neuroprotectants</td>
</tr>
<tr>
<td>US20040049059</td>
<td>October 16, 2001</td>
<td>March 11, 2004</td>
<td>Adam Mueller</td>
<td>Method for producing an extract from cannabis plant matter, containing a tetrahydrocannabinol and a cannabinol and cannabis extracts</td>
</tr>
<tr>
<td>US2008103193</td>
<td>October 26, 2006</td>
<td>May 1, 2008</td>
<td>Trevor Percival Castor</td>
<td>Methods for making compositions and compositions for treating pain and cachexia</td>
</tr>
<tr>
<td>US20080241339</td>
<td>March 28, 2007</td>
<td>October 2, 2008</td>
<td>California Natural Products</td>
<td>Hemp food product base and processes</td>
</tr>
<tr>
<td>US20100216872</td>
<td>September 26, 2008</td>
<td>August 26, 2010</td>
<td>Heinz Letzel</td>
<td>Plant extract from low-THC cannabis for the treatment of disease</td>
</tr>
<tr>
<td>US20110098348</td>
<td>April 9, 2009</td>
<td>April 28, 2011</td>
<td>GW Pharma Ltd.</td>
<td>Cannabis sativa plants rich in cannabichromene and its acid, extracts thereof, and methods of obtaining extracts therefrom</td>
</tr>
<tr>
<td>US20120311744</td>
<td>June 6, 2012</td>
<td>December 6, 2012</td>
<td>Erich E. Sirkowski</td>
<td>Marked cannabis for indicating medical marijuana</td>
</tr>
<tr>
<td>US20130109747</td>
<td>June 1, 2012</td>
<td>May 2, 2013</td>
<td>GW Pharma Ltd.</td>
<td>Pharmaceutical formulation</td>
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<tr>
<td>US20140243405</td>
<td>September 14, 2012</td>
<td>August 28, 2014</td>
<td>Otsuka Pharmaceutical Co., Ltd</td>
<td>Pharmaceutical composition comprising the phytocannabinoids cannabidiol and cannabidiol</td>
</tr>
<tr>
<td>US20140298511*</td>
<td>March 17, 2014</td>
<td>October 2, 2014</td>
<td>Biotech Institute, LLC</td>
<td>Breeding, production, processing, and use of medical cannabis</td>
</tr>
</tbody>
</table>

Abbreviation: THC, delta-9-tetrahydrocannabinol.

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**EFFECTS OF MINDFULNESS ON CANCER RECOVERY**

**What Is Mindfulness?**

Mindfulness is the practice of fully paying attention to the present and maintaining awareness, with nonjudgment, emotional balance, and openness. It includes both formal and informal meditation practices to engage an individual’s relationship to experience. Mindfulness is rooted in Buddhism, and because of its purpose to improve suffering and encourage compassion, it has a potential role in medicine.
Instead of focusing on the distress itself, mindfulness-based programs train individuals to refine their awareness of health and their response to various forms of distress. Mindfulness practices can help individuals recognize their usual conditioned ways of reacting and strengthen their ability to cope with disability or pain. This shift in their relationship to their thoughts, feelings, and body sensations, called decentering or reperceiving, can lead to optimization in prevention and recovery from illness. Different mind-body interventions, including but not limited to relaxation, biofeedback, hypnosis, yoga, art therapy, music therapy, combined movement and meditation therapy (e.g., tai-chi and qigong), have been used to focus on the interactions among the brain, mind, body and behavior to improve overall health and physical functioning.

Mindfulness-based programs (MBPs) use these fundamental principles to involve participants in sustained rigorous training in mindfulness meditation practices to develop awareness and understanding. A distinguishing characteristic of MBP is the systematic training for both teachers and participants in formal and informal mindfulness meditation practices. Original MBPs include mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy (MBCT). MBSR is a group program that was developed within a medical framework in 1979 by Kabat-Zinn to introduce formal and informal mindfulness in clinical settings. MBSR is traditionally scheduled over eight weekly sessions lasting 2.5 hours each. Fundamental principles include three formal mindfulness meditation practices: body scan, sitting meditation, and mindful movement. Daily home practice consists of 40 minutes of guided mindfulness in everyday activities. MBSR has shown effectiveness in enhancing mental health outcomes and reducing stress in people with chronic health problems.

MBCT, originally developed for people in remission from major depression, integrates MBSR’s core components with aspects of cognitive therapy to prevent recurrence or relapse of depression. It introduced the mini-meditation, or 3-minute breath space. Compared with MBSR, MBCT has smaller class sizes and participants have similar disorders. Other MBPs with similar theoretical ideas and mindfulness meditation practices have since been developed, reaching a broad population and various settings, including hospitals, schools, and prisons.

After changes to the MBSR program were made in 2000 to better target a cancer population, MBSR has been the most used practice in studies of mindfulness in oncology. The study of the effectiveness of MBSR in patients with cancer has been growing because it is well known that cancer is frequently associated with psychological suffering and stress. After the initial diagnosis of cancer or recurrence, 10% to 20% of patients eventually develop depression and anxiety, which can lead to worsening of their overall health. They have high degrees of sleep disturbances, chronic fatigue, and trauma. Greater than 45% of patients with cancer have reported that the emotional distress of cancer was more difficult to manage than the physical effects. Patients with cancer may have a higher rate of complementary therapy use to alleviate these effects; in contrast, oncologists use these complementary therapies less often than do other specialists. Early studies of MBSR in oncology have shown potential in improving mood, coping, pain, nausea, fatigue, and sleep disturbance. More recently, randomized controlled trials and meta-analyses have explored the effects of the MBP intervention in the oncology population.

Potential Benefits of MBPs

In 1982, Kabat-Zinn first reported the effectiveness of MBSR intervention in patients with chronic pain of 6 months’ to 48 years’ duration. After patients completed training, their perceived pain decreased significantly, with 50% of patients reporting a reduction of at least 50%. Speca and colleagues then adapted the MBSR program in 2000 to better address the needs of patients with cancer. The study enrolled 109 patients with various types of cancer. The MBSR group experienced improvements of 65% in mood disturbance and 31% in stress symptoms. Other positive effects included acceptance of pain, severity of general medical symptoms, physical functions, and ability to cope with daily life.

A growing body of evidence suggests that MBPs may help to reduce psychological symptoms of stress and anxiety, especially in women with breast cancer. Randomized controlled trials using MBSR or MBCT have shown improvements in anxiety and fear of recurrence, depression and distress, breast- and endocrine-related quality of life, and overall well-being in patients with breast cancer. A systematic review and meta-analysis by Haller and colleagues identified 10 RCTs on MBSR and MBCT in 1,709 women with breast cancer. It concluded that MBSR and MBCT are safe and effective at reducing anxiety and depression 6 to 12 months after intervention. Long-term studies are needed.

MBSR has also demonstrated improvement in immune function and physical effects of poor sleep and fatigue. Small nonrandomized trials in patients with breast or prostate cancer have shown marked decreases in cortisol and re-establishment of natural killer cell activity and cytokine production levels, a reduction in T-helper 1 (proinflammatory) cytokine levels, decreased blood pressure, and decreased subjective stress symptoms. However, changes in objective and subjective measures were greatest for those who were more distant from their cancer diagnosis and treatment and did not correlate with the amount of time spent practicing MBSR techniques. Studies have shown mixed effects on the ability of MBSR to improve insomnia, with some studies showing improvement in the insomnia severity index and objective measures, such as actigraph measurements and number of waking bouts, whereas other studies showed no improvement in subjective or objective measures related to sleep. However, these trials are limited by lack of a standardized definition of sleep disorder, lack of long-term follow-up, nonactive control groups, and nonvalidated subjective and objective sleep measures.
MBPs in Gynecologic Cancers

Many of the MBP studies in patients with gynecologic cancer have focused on its effect on sexual function. Studies have used many MBP practices, including MBCT, psycheducation, and even online mindfulness meditation instruction, for patients with gynecologic cancer.\(^9^3\) Results from these small studies have shown improvement in sexual desire, arousal, orgasm, satisfaction, and sexual distress, with effects lasting up to 6 months.

Quality-of-life studies using MBCT or other MBPs, including bio-behavioral therapy, in patients with breast and gynecologic cancer have shown significant improvements in distress, anxiety, negative affect, post-traumatic growth, mindfulness, and overall quality of life when measured by using validated surveys.\(^9^0,^9^2\) One of the studies supplemented mindfulness, and overall quality of life when measured by distress, anxiety, negative affect, post-traumatic growth, and even online mindfulness meditation instruction, for patients with gynecologic cancer.\(^8^7,^8^9\) Results from these small studies have shown improvement in sexual desire, arousal, orgasm, satisfaction, and sexual distress, with effects lasting up to 6 months.

One of the studies supplemented the subjective findings with objective measures showing significant decreases in morning cortisol levels and resting heart rate.\(^9^0\) An internet-based strategy specifically tailored to ovarian cancer survivors using a combination of MBSR, cognitive-behavior stress management, and acceptance and commitment therapy showed marked improvements in perceived stress and ovarian cancer-specific quality of life.\(^9^3\)

Limitations of MBP Studies and Areas for Future Research

Because of the disparity of study designs and measures, it is hard to compare effectiveness across different mindfulness-based interventions. Even studies of well-defined practices, such as MBSR and MBCT, often deviate from the intervention as originally described. The results of many studies are difficult to interpret because of small sample sizes, lack of control groups, short follow-up, and methodologic issues, including the fact that patients receiving antidepressant medications are often excluded.\(^5^7\) Participants are primarily white, female, well-educated and middle-aged, with breast cancer being the most common diagnosis, and thus are not representative of all individuals with cancer.\(^5^7\) Studies are needed to determine the best form of delivery of mindfulness interventions and for whom it is intended.\(^5^9\) Data on the optimum length of contact time and the use of home practice are lacking.\(^6^2\) Because of the limited number of randomized clinical trials and qualitative studies, it is also unclear whether mindfulness is the operator of change. To further understand how mindfulness could improve outcomes in patients with cancer, endpoints should correlate physiologic responses and quality of life.\(^6^2\)

Role of MBPs for Cancer Recovery

Because patients with cancer often suffer emotional and psychological distress during and after treatment, it is important to address these issues to improve patients’ overall well-being. Mindfulness-based practices have potential to integrate with primary care and oncology services to increase the ability to cope with pain and chronic illness, reduce stress in patients, and foster compassion. The delivery of mindfulness in cancer is not limited to MBSR and MBCT; in fact, modifications of the original MBSR and MBCT protocols to better target the problem or specific populations are encouraged. Many areas are yet unexplored, and there is a continued need for rigorous, high-quality studies to investigate mechanisms, effectiveness, and implementation.

References


The Epigenetic Landscape in the Treatment of Gynecologic Malignancies

Ramez N. Eskander, MD

OVERVIEW

The care of patients with advanced-stage or recurrent endometrial, ovarian, and cervical cancer remains clinically challenging. Despite the identification of novel therapeutics and advancements in supportive care, survival outcomes have been relatively unchanged over the past decade. In addition to established genomic alterations and the contributions of the tumor microenvironment to cancer progression, epigenetic mechanisms have emerged as important contributors to gynecologic cancer progression. DNA methylation, histone modification, and noncoding RNA expression may be important contributors to disease initiation and progression and may represent novel therapeutic targets. This article reviews the epigenetic landscape of endometrial, ovarian, and cervical cancer, describing the state of the science and discussing potential clinical applications. To date, the role of epigenetic drugs in the treatment of gynecologic cancers remains unclear, although continued progress may inform future treatment modalities.

With an improved understanding of the molecular landscapes of ovarian, uterine, and cervical cancer, an interest in targeted therapies has emerged. This molecular granularity has translated into U.S. Food and Drug Administration (FDA) approvals of the antiangiogenic agent bevacizumab and of the PARP inhibitors (niraparib, rucaparib, olaparib), after a nearly 10-year interval which saw limited progress in patients suffering from recurrent cervical and ovarian cancer.

In an effort to expand on the above, investigators have turned their attention beyond traditional genomic mutations, exploring the role of the epigenome on cancer progression, in an attempt to identify novel therapeutic strategies. Epigenetics is defined as changes in gene expression that are not due to alterations in DNA sequence. The principal epigenetic changes identified, and studied, to date include the following: (1) DNA methylation, (2) histone modification, and (3) microRNA (miRNA) inhibition. This epigenetic reprogramming of gene expression has been clearly identified as a driver in malignant transformation and cancer propagation.

Traditionally, malignant transformation is thought to arise from the activation of oncogenes or the inactivation of tumor suppressor genes via germline or somatic mutations. More recently, changes in the epigenome have been identified, which contribute to the initiation and progression of cancer. Approximately 40% of genes harbor DNA promoter regions rich in cytosines that precede guanines (CpGs), which, when methylated, result in transcriptional repression. This process, catalyzed by DNA methyltransferases (DNMTs), may occur in the promoter regions of tumor-suppressor genes, resulting in oncogenic transformation. This paradigm has been well described for the retinoblastoma (Rb), p16, hMLH1, and BRCA1 tumor-suppressor genes. In humans, the three known DNMTs include DNMT1, DNMT3A, and DNMT3B. DNMT1 is responsible for maintaining hemimethylation of DNA during replication, whereas DNMT3A and DNMT3B can catalyze de novo DNA methylation.

Beyond DNA CpG island methylation, epigenetic regulation may occur via histone modification. Histones are a group of proteins responsible for DNA packaging and are amenable to modification on their N-terminal residue. Multiple complex combinations have been described, including methylation, acetylation, and phosphorylation occurring at lysine, arginine, or serine residues. Importantly, acetylation and methylation of histones can result in multiple downstream effects affecting transcription, DNA replication, and repair, as well as chromosome organization. Histone acetylation is generally associated with transcriptional activation, whereas the effect of methylation varies and depends on the amino acid residue and its location. In an analogous manner to DNA promoter methylation, histone modification via hypoxacetylation, and methylation of lysine-9 on histone H3 or lysine-27, can lead to transcriptional repression. Conversely, acetylation of histone H3 and H4...
and methylation of lysine-4 residue of histone H3 have been associated with gene activation. These processes are mediated by a family of proteins, including histone acetyltransferases, histone deacetylase (HDAC), histone demethylases, and histone methyltransferases.

More recently, the influence of noncoding RNAs, including miRNA, on transcriptional regulation has been described. These small 22-nucleotide sequences regulate gene expression via binding at the 3′ untranslated region, resulting in the formation of RNA-induced silencing complexes, with inhibition of translation or RNA destabilization. Evaluation of both normal and cancer tissue specimens suggests that miRNA downregulation is associated with tumorigenesis and that miRNA may serve a tumor suppressor function. As an example, the downregulation of the let-7 family of miRNAs has been linked to lung cancer progression and is thought to be mediated by RAS oncogene activation.

The paradigm of epigenomic therapeutics has been most extensively examined in the hematologic arena, in which the FDA has approved six agents as antineoplastic drugs: vorinostat (HDAC inhibitor), romidepsin (HDAC inhibitor), 5-azacytidine (DNA methyltransferase inhibitor), decitabine (DNA methyltransferase inhibitor), and ruxolitinib (JAK1/2 inhibitor).

In patients with gynecologic malignancies, epigenetic silencing has been hypothesized to be a driver of cancer progression, with differential methylation profiles in endometrial, ovarian, and cervical cancer specimens. Given the substantial unmet clinical need, translational scientists and clinical trialists are exploring the implications of the epigenome and the therapeutic efficacy of novel epigenetic agents on oncologic outcomes in patients with gynecologic cancer.

**ENDOMETRIAL CANCER**

Endometrial cancer continues to be the most common gynecologic malignancy in the United States and is the only cancer of the female genital tract with a rising incidence and mortality. In 2018, it is estimated that there will be 62,230 new cases and 11,350 deaths. Despite the excellent prognosis in patients with early-stage disease, those with metastatic or recurrent endometrial cancer have limited therapeutic options. Since the completion of Gynecologic Oncology Group (GOG) protocol 177, which explored the triplet regimen of paclitaxel, doxorubicin, and cisplatin in patients with advanced-stage and recurrent endometrial cancer, there have been limited therapeutic advancements. GOG protocol 209 was a subsequent phase III clinical trial comparing the combination regimen of carboplatin plus paclitaxel to the combination of paclitaxel, doxorubicin, and cisplatin. This study enrolled more than 1,300 patients and demonstrated less toxicity and a noninferior progression-free survival and overall survival with the doublet regimen of carboplatin plus paclitaxel. Furthermore, second-line chemotherapy options for endometrial cancer are notably less effective, with Megace (Bristol-Myers Squibb) being the only FDA-approved agent in this setting.

Growing evidence suggests that epigenetic alteration, in the form of aberrant DNA methylation, is a widespread and early alteration in endometrial cancer progression that affects the expression of numerous important genes. Molecular analysis of endometrial tumorigenesis in 110 cancer specimens and 62 controls identified promoter hypermethylation, and transcriptional repression, in 24 tumor suppressor genes, with progressive methylation from simple hyperplasia to complex hyperplasia and ultimately carcinoma. Furthermore, in DNA mismatch repair (MMR) gene mutation carriers, MMR and methylation defects were identified more than 10 years before the diagnosis of endometrial cancer. To date, DNA promoter methylation has been identified in several gene targets in endometrial cancer, potentially contributing to carcinogenesis (Table 1).

**TABLE 1. Epigenetic Targets via Promoter Hypermethylation in Endometrial Cancer**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Gene Name</th>
<th>Function</th>
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<tr>
<td>hMLH1</td>
<td>Human Mut-L homolog 1</td>
<td>DNA mismatch repair gene</td>
</tr>
<tr>
<td>APC</td>
<td>Adenomatous polyposis coli</td>
<td>Regulation of cell cycle and apoptosis, cell adhesion, signal transduction</td>
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<tr>
<td>RASSF1A</td>
<td>Ras-associated domain family protein 1</td>
<td>Cell cycle regulation, cellular adhesions, apoptosis</td>
</tr>
<tr>
<td>PS3</td>
<td></td>
<td>Regulates cellular proliferation, apoptosis induction, DNA repair</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatase and tensin homolog</td>
<td>Regulates cellular proliferation and apoptosis</td>
</tr>
<tr>
<td>CDH1</td>
<td>E-Cadherin</td>
<td>Epithelial cell adhesion</td>
</tr>
<tr>
<td>ERα</td>
<td>Estrogen receptor alpha</td>
<td>Regulation of proliferation</td>
</tr>
<tr>
<td>PR-B</td>
<td>Progesterone receptor</td>
<td>Regulation of proliferation</td>
</tr>
<tr>
<td>p16</td>
<td>Cyclin-dependent kinase inhibitor 2A</td>
<td>Cell cycle regulation</td>
</tr>
</tbody>
</table>

**PRACTICAL APPLICATIONS**

- The management of advanced-stage or recurrent gynecologic cancer remains a clinical challenge.
- Epigenetic changes have been identified as potential drivers of cancer progression across multiple tumor types, including ovarian, endometrial, and cervical cancer.
- A better understanding of these epigenetic changes may help identify novel therapeutic paradigms and improve outcomes.
- To date, responses with the use of single-agent epigenetic drugs, as well as combination regimens, have been clinically disappointing.
- It will be important to identify potential predictors of response with the use of epigenetic to maximize efficacy and reduce toxicity.
It is well established that germline mutations in DNA mismatch repair genes (hMLH1, hMSH2, hMSH3, hMSH6, and hPMS2) result in Lynch syndrome, with an increased risk for endometrial cancer. More recently, hMLH1 promoter hypermethylation has been reported in up to 40% of endometrial cancer specimens, resulting in transcriptional repression and a microsatellite-high phenotype. This finding is particularly relevant given the recent success of immune checkpoint inhibition in patients with MMR-deficient, recurrent endometrial cancer. Building on initial data published by Le and colleagues, Fader and colleagues presented an expanded cohort of patients with MMR-deficient and recurrent or persistent endometrial cancer treated with single-agent treatment with pembrolizumab. All 10 patients had received at least one prior line of systemic chemotherapy and up to four previous regimens. The authors reported an overall response rate of 70% (95% CI, 21%–86%; seven patients), with two complete responses and five partial responses. The disease control rate, or “clinical benefit” rate (complete response + partial response + stable disease), was 80% (eight patients). The 12-month overall survival rate was 89%, and the median overall survival was not yet reached at time of reporting. Importantly, microsatellite instability (MSI) status was determined by using standard-of-care MMR immunohistochemistry testing for hMLH1, hMSH2, hMSH6, and hPMS2. Patients lacking expression of DNA MMR proteins were classified as MSI-high, consistent with prior studies reporting concordance rates greater than 90% between MMR immunohistochemistry and MSI polymerase chain reaction. In the trial, hMLH1 promoter hypermethylation was not evaluated in patients lacking immunohistochemistry expression of hMLH1 or hPMS2.

Most recently, after review of pooled data from five uncontrolled, open-label, multicohort, multicenter, single-arm trials, single-agent pembrolizumab was approved for the treatment of MMR-deficient (MSI-high) solid tumors that progressed following prior therapy, with no alternative treatment options. This disease site–agnostic approval, issued by the FDA on May 23, 2017, was the first of its kind, reflecting the clinical relevance of checkpoint inhibition in patients with limited therapeutic options. Across all five trials, the efficacy analysis showed an overall response rate (ORR) of 39.6% (95% CI, 31.7%–47.9%) with a complete response rate of 7.4% and a partial response rate of 32.2%. At the time of data cutoff, median duration of response had not yet been reached (range, 1.6+ to 22.7+ months), with 78% of responding patients having responses of 6 months or longer. Of the 149 patients in the pooled analysis, 14 had recurrent endometrial cancer, with a reported ORR of 36% (duration of response range, 4.2+ to 17.3+ months), surpassing historical controls in this pretreated patient population.

In the recurrent disease setting, a variety of therapeutic approaches using various hormonal agents have been examined, with a clinical benefit rate approaching 40%. Hormonal therapy is appealing in this patient population, principally because of ease of administration as well as the beneficial therapeutic index. Despite robust preclinical and biologic rational for endocrine therapy, these agents are commonly effective for a brief period, with patients developing resistance and progressive disease. It is hypothesized that resistance is a result of progesterone receptor downregulation and silencing of signal transduction. This was exemplified in GOG protocol 0211, a preoperative window-of-opportunity trial in women with endometrial cancer. After the diagnosis of biopsy-proved disease, women were enrolled to receive medroxyprogesterone acetate 21 to 24 days before surgery. The authors reported a 64% partial response rate and one complete response among 59 women. Interestingly, GOG-0211 illustrated a downregulation of progesterone receptor after exposure to medroxyprogesterone. In preclinical models, progesterone receptor downregulation is thought to result from promoter CpG hypermethylation and gene silencing.

The preceding results have since catalyzed the development and activation of NRG-GY011, a randomized surgical window pilot investigation of the relationship of short-term medroxyprogesterone acetate therapy compared with medroxyprogesterone acetate plus entinostat on the morphologic, biochemical, and molecular changes in primary endometrioid adenocarcinoma of the uterine corpus. The selection of entinostat, an HDAC inhibitor, in protocol design was driven by its oral formulation and ease of administration, robust data suggesting its efficacy in upregulating and maintaining progesterone receptor levels, and cellular differentiation. The results of this trial may subsequently inform the utility of a combinatorial approach, hormonal therapy plus epigenetic modifier, in patients with recurrent endometrial carcinoma.

In addition to the above, the ARID1A gene has been identified as a frequently mutated tumor suppressor in several gynecologic malignancies. ARID1A encodes the BAF250a protein, a member of the SWI/SNF complex, participating in chromatin remodeling and transcriptional regulation. Aberrations in chromatin remodeling have been identified in approximately 20% of all human cancers. Specifically, the SWI/SNF complex is involved in activation or inhibition of transcription and plays a crucial role in carcinogenesis. More recently, studies have shown that ARID1A mutations are involved in carcinogenesis via the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) pathway, with resultant cellular proliferation and inhibition of apoptosis.

Genetic studies have revealed an evolutionarily conserved antagonistic relationship between the SWI/SNF complex and polycomb group proteins. The loss of SWI/SNF complex subunits (ARID1A, SMARCB1, and SMAR4A) results in unopposed zeste homolog 2 (EZH2) activity, promoting carcinogenesis, and oncogenic transformation.

ARID1A mutations have been identified in up to 47% of low-grade endometrioid endometrial carcinomas, 60% of high-grade endometrioid adenocarcinomas, 11% of serous adenocarcinomas, and up to 24% of carcinosarcomas. An association between loss of ARID1A protein expression and activation of the PI3K/AKT pathway has also been
detailed. Mutations of PTEN and PIK3CA frequently occur in endometrial carcinomas with ARID1A mutation, and it is hypothesized that these ARID1A mutations induce aberrant activation of the PI3K pathway.\textsuperscript{30} Additionally, investigators have explored the possibility that ARID1A mutation may result in defective MMR, resulting in MSI and greater tumor mutational burden. A strong association between ARID1A loss and sporadic MSI is thought to result from epigenetic silencing of MLH1.\textsuperscript{34}

Given the data outlined above, investigators are looking to evaluate the activity of single-agent azacitidine (an oral EZH2 inhibitor) in patients with recurrent endometrioid adenocarcinoma. This epigenetic approach seeks to capitalize on the oncogenic addiction of ARID1A-mutated endometrial cancers on EZH2 activity. Translational endpoints will include BAF250a immunohistochemistry expression on tumor samples, as well as genomic sequencing of 467 other genes, including alternate components of the SWI/SNF pathway (e.g., ARID1B, ARID2, SMARCA4, SMARCB1, SMARCD1, and PBRM1).

**OVARIAN CANCER**

Epithelial ovarian cancer accounts for 25% of all malignancies affecting the female genital tract and remains the most fatal gynecologic malignancy. In the United States, a projected 22,240 new cases will be diagnosed in 2018, with 14,070 deaths.\textsuperscript{20} Advanced-stage epithelial ovarian cancer is managed with primary or interval surgical cytoreduction and combination platinum- and taxane-based chemotherapy.\textsuperscript{35} In some centers, use of the intraperitoneal-intravenous drug delivery route has persisted despite conflicting clinical trial results.\textsuperscript{30} Conversely, a weekly, dose-dense schedule for paclitaxel gained popularity after an overall survival advantage was reported in a Japanese GOG clinical trial, with the more recent ICON-8 results once again questioning this approach.\textsuperscript{37,38} Irrespective of cytotoxic regimen and mode of administration, the greatest hurdles in the treatment of patients with advanced-stage ovarian cancer remains acquired drug resistance and selection of platinum-resistant clones.\textsuperscript{39} Thus, the development of active, tolerable, noncytotoxic drugs has emerged as a priority in epithelial ovarian cancer research.

As discussed earlier, the evolution of our understanding of the molecular landscape of ovarian cancer has facilitated drug development, with the recent FDA approval of three separate PARP inhibitors in the maintenance therapy and recurrent settings. These promising advances have additionally prompted the investigation of alternate therapeutics, including potential epigenetic targets. Perhaps the most notable epigenetic changes identified in ovarian cancer are the methylation and silencing, of the tumor suppressors BRCA1 and hMLH1, both responsible for DNA damage repair.\textsuperscript{40,41} In a recent large case-control study of more than 5,000 women, BRCA1 promoter methylation was identified more frequently in patients with ovarian cancer than controls (6.4% vs. 4.2%; age-adjusted odds ratio, 1.83 [95% CI, 1.27–2.63]).\textsuperscript{42} Consistent with prior data from *The Cancer Genome Atlas*, elevated methylation was restricted to patients with high-grade serous ovarian cancer (9.6%; odds ratio, 2.91 [95% CI, 1.85–4.56]), in contrast to 5.1% and 4.0% of patients with nonserous and low-grade serous ovarian cancer, respectively. Perhaps the most thought-provoking aspects of this study include identification of BRCA1 methylation in newborn cord-blood samples, suggesting that methylation may be an embryonic event that affects cancer risk throughout life.\textsuperscript{42}

In an effort to improve clinical outcomes, investigators have examined the effect of DNMT inhibitors on chemotherapeutic sensitivity in preclinical models, and the potential for reversal of platinum and taxane resistance.\textsuperscript{43,44} Subsequently, in a phase I clinical trial, low-dose decitabine was given in combination with carboplatin in patients with recurrent, platinum-resistant ovarian cancer.\textsuperscript{45} Decitabine was administered intravenously daily for 5 days, before carboplatin area under the curve of 5 on day 8 of a 28-day cycle. A standard 3 + 3 dose escalation design was used, with decitabine tested at two dose levels: 10 mg/m\textsuperscript{2} (seven patients) or 20 mg/m\textsuperscript{2} (three patients). Dose-limiting toxicity at the 20-mg/m\textsuperscript{2} dose was grade 4 neutropenia (two patients), and no dose-limiting toxicities were observed at 10 mg/m\textsuperscript{2}.\textsuperscript{45} Ten heavily pretreated patients were enrolled (median of five prior lines of therapy), with nine completing at least one cycle of therapy. One complete response was observed, and three additional patients had stable disease for 6 months or more. Translational on-treatment assessment of methylation using polymerase chain reaction demonstrated reduced global methylation on days 8 and 15 when compared with day 1.\textsuperscript{45}

The biologic activity seen in this early phase I study prompted the assessment of alternate epigenetic agents, specifically HDAC inhibitors, in patients with recurrent ovarian cancer. In a phase II clinical trial, Dizon and colleagues examined the activity of belinostat in combination with carboplatin in women with platinum-resistant, recurrent ovarian cancer.\textsuperscript{46} A total of 27 eligible and evaluable women were enrolled in the trial and treated with 1,000 mg/m\textsuperscript{2} of belinostat daily for 5 days with carboplatin area under the curve of 5 on day 3 of a 21-day cycle. The median number of cycles given was two (range, 1 to 10). One patient had a complete response and one had a partial response (due to lack of normalization of her Ca-125 level), for an ORR of 7.4% (95% CI, 0.9%–24.3%), resulting in closure of the trial after the first stage due to drug inactivity.\textsuperscript{46} Twelve patients (44.4%) had stable disease as their best response. Grade 3 and 4 adverse events occurring in more than 10% of treated patients were uncommon and were limited to neutropenia (22.2%), thrombocytopenia (14.8%), and vomiting (11.1%). Unfortunately, single-agent belinostat failed to show clinical responses in a cohort of patients with platinum-resistant epithelial ovarian cancer, despite the accumulation of acetylated histones H3 and H4 in peripheral blood mononuclear cells.\textsuperscript{37}

In another study, once again conducted in the platinum-resistant setting, belinostat was used in combination with
CARCINOMA

After the identification of cisplatin as an effective drug in the treatment of cervical cancer, many effective single-agent and combination drug regimens were identified with improved response rates, but no overall survival advantage.55-71 The poor oncologic outcome in this patient population has driven the exploration of novel treatment paradigms.72 Most recently, GOG protocol 240 was completed, illustrating a significant improvement in overall survival (17 vs. 13.3 months; p = .007) with the incorporation of the antiangiogenic agent bevacizumab to a chemotherapy backbone, without a deterioration in quality of life.73-76 This milestone represented the first time a targeted agent resulted in an overall survival advantage in the gynecologic cancer arena, resulting in FDA approval of bevacizumab in the treatment of advanced-stage or recurrent cervical cancer.77

Cervical cancer is unique among gynecologic cancers because several risk factors are well established, and the causative agent, human papillomavirus (HPV), is known. This was confirmed in the molecular characterization of cervical cancer, where 95% specimens were found to be HPV positive.2 High-risk HPV infection alone is not sufficient for malignant transformation, and it is hypothesized the alternate genetic and epigenetic factors are required for carcinogenesis.78 The most extensively studied epigenetic changes in cervical carcinogenesis include DNA methylation and histone modification.

Principal targets of methylation include the p16 protein, a cyclin-dependent kinase inhibitor, which traditionally functions as a tumor suppressor. Following HPV infection, early p16 inactivation has been identified, with progressive methylation in more advanced tumors.79 In addition to the p16 tumor suppressor, fragile histidine triad gene (FHIT), cyclin A1 (CCNA1), DAPK1, and Ras-associated domain family 1 isoform A (RASSF1A) are targets of DNA promoter methylation and transcriptional repression.79 HPV-related promoter hypermethylation has also been identified in genes related to cellular differentiation, proliferation, adhesion, and cell signaling (Sidebar.).

TABLE 2. Frequency of ARID1A Mutations in Endometrioid and Clear Cell Ovarian Cancer

<table>
<thead>
<tr>
<th>Study Author</th>
<th>Endometrioid (%)</th>
<th>Clear Cell (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wiegand et al50</td>
<td>30</td>
<td>46</td>
</tr>
<tr>
<td>Rambau et al51</td>
<td>48</td>
<td>–</td>
</tr>
<tr>
<td>Takeda et al52</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>Chene et al53</td>
<td>22</td>
<td>47</td>
</tr>
<tr>
<td>Mao and Shih54</td>
<td>30</td>
<td>57</td>
</tr>
<tr>
<td>Ayhan et al55</td>
<td>55</td>
<td>75</td>
</tr>
<tr>
<td>Lowery et al56</td>
<td>48</td>
<td>41</td>
</tr>
</tbody>
</table>

*Expression assessed by BAF250a immunohistochemistry alone.
The contribution of histone modification has also been evaluated, with increased expression of HDACs in cervical carcinoma. Parenthetically, in an alternate cell line, histone deacetylation, resulting in canonical Wnt antagonist DICKKOPF-1 is downregulated as a result of target genes. In cervical cancer HeLa cell lines, the Wnt compact chromatic and transcriptional repression of cell 1.

cervical carcinoma. Histone deacetylation results in been evaluated, with increased expression of HDACs in cell.

methylaƟ on. of tumor suppressor genes, without aff  ecƟ  ng global DNA

deralazine at doses between 50 and 150 mg/d was well tol-

lored intervenƟ ons. This may maximize therapeuƟ c benefi t, while limiting toxicity, given the potential off-target effects of this drug class.

CONCLUSION

The role of epigenetic drugs in the treatment of advanced-stage or recurrent ovarian, endometrial, and cervical cancer remains unclear. Despite substantial preclinical rationale, limited response rates have been observed to date. The interplay between the genome and epigenome in cancer progression is undoubtedly complex and multifactorial, with both environmental and heritable components. Furthermore, the relative contribution of DNA methylation/hypomethylation, histone modification, and miRNA expression on gynecologic cancer genesis continues to be debated.

Ultimately, targeted therapeutics and combined approaches will require identification of predictive biomarkers to enrich for patient populations more likely to respond to tailored interventions. This may maximize therapeutic benefit, while limiting toxicity, given the potential off-target effects of this drug class.

References


Radiotherapy as cancer treatment remains an effective option for patient cure and palliation. It helps cure some cancers, such as localized breast, cervical, and prostate cancer. It provides long-lasting control for palliation of many others. More than 16.6 million American pediatric and adult cancer survivors are estimated alive as of January 1, 2018, half of whom underwent radiotherapy as cancer treatment at one time or another. Steady federal support of practice-altering basic science and clinical research ultimately has translated into enhanced cures and reduced morbidity. New insights in cancer biology, radiobiology, and radiochemistry have repositioned radiopharmaceutical therapies at the leading edge of personalized medicine oncology research. Existing and forthcoming programmatic initiatives at the National Cancer Institute (NCI) intend to prominently boost radiopharmaceutical clinical development in an era of personalized medicine.

Forecasts for radiopharmaceutical trial success are better now than before. Yet the landscape for success has changed. Oncology clinical trials currently enrich for molecularly selected patient populations in an effort to gain supportive evidence for investigational agents in disease-specific treatment indications. This strategic approach can set the stage for rapid and efficient introduction of new drug therapies to patients. New or repurposed radiopharmaceutical therapies should adopt similar drug strategies (1) to appeal to patients and (2) to broaden clinical utility. And here a radiopharmaceutical therapy should be thought of as a drug therapy. Existing NCI Cancer Therapy Evaluation Program (CTEP) initiatives consider a radiopharmaceutical therapy to be a radionuclide delivered by vein, injection, or ingestion intending to irradiate targeted cancer cells while minimizing irradiation dose to nearby normal cells (Fig. 1). There are factors that make it reasonable to consider radiopharmaceutical therapies drug like and amenable to development similar to that of investigational drugs.

Radiopharmaceuticals act by emitting short-range DNA-damaging ionizing radiation to overwhelm a cancer cell’s DNA damage response (DDR), much like highly selective drugs inactivate cancer target proteins. They have quantifiable pharmacokinetic exposures and elimination half-lives. Typically, their prescription doses are fixed by patient body weight (or body surface area, depending on the agent). Last, they have predictable organ toxicities. By considering these agents to be drugs from the outset, CTEP contends that radiopharmaceutical therapies can follow an easier programmatic path for clinical development to address unmet patient need. This also provides a clearer vision for regulatory approval so that important radiopharmaceutical therapies reach patients earlier. Through one of its initiatives, the NCI Small Business Innovation Research Development Center reviewed 21 next-generation radiopharmaceutical cancer technology projects between 2015 and 2017. Nineteen projects have been funded so far. Research on radiopharmaceutical candidate drugs continues to be needed clinically.
For an audience unfamiliar with radiotherapy clinical development at CTEP, this article provides perspective on a modern approach to radiopharmaceutical therapies in the era of personalized medicine. Prior clinical experience, gained in radiopharmaceutical therapy for women with ovarian cancer, frames current and future initiatives.

RADIOPHARMACEUTICAL EXPLOITABLE DDRS IN CANCER
Exploitable DNA Damage Responses
A hallmark of cancer cells is the loss of one or more DDRs. A cell's response to damaged DNA includes base excision repair, nucleotide excision repair, mismatch repair, homologous recombination repair, and nonhomologous end joining. Each repair pathway is reviewed elsewhere. Loss of one or more DDR pathways leads to greater reliance on those that remain. A cancer cell heavily reliant on one DDR pathway is more prone to die when its survival DDR pathway is blocked. This is known as synthetic lethality. An exploitable DDR survival pathway, whereby drug monotherapy brings about success alone, is rare. That is why the term “synthetic lethality” can lead to confusion. Another definition of synthetic lethality describes synergy or additivity when a genetic lesion elevates sensitivity, but a second cytotoxic agent is required to kill cancers. This scenario renders drug monotherapy less likely to be effective. Antibody-radionuclide conjugates might be particularly attractive in this case (Fig. 1).

A third definition of synthetic lethality explains the instance in which two or more agents are combined for synthetic lethal effects when a genetic mutation of known pathologic significance is present. This often is termed “contextual synthetic lethality.” Because cytotoxic drug combination partners are acting independently, therapeutic index falls. If effective combinations are not tested together, clinical development of one or the other agent might lag. Meeting definition 1 or 2 is a goal in oncology research. Probably the best-known DDR-deficient cancers that fit the first definition are those that harbor faulty elements of homologous recombination repair. This condition arises from inactive breast- and ovarian-associated tumor suppressor genes $BRCA1$ and $BRCA2$. Cells with intact $BRCA1$ and $BRCA2$ are capable of sister chromatid recombination and...
repair. This process involves nuclear RAD51 foci. Cancers with defective BRCA1 and BRCA2 cannot recruit homologous recombination repair proteins. Therefore, sister chromatid recombination repair is compromised. And error-prone non-homologous end joining or other repair mechanisms take over and predominate as the survival DDR pathway. Cancers with faulty homologous recombination repair might over rely on PARP to fix incurred DNA single-strand breaks. PARP inhibition by drugs brings about chemical synthetic lethality. The strategy of PARP inhibition is effective, as at least five PARP inhibitors are in late phase clinical development for patients with ovarian cancer, and three have been licensed for specific clinical indications.

Better understanding of cancer and normal cell radiobiology is important for radionuclide clinical development when cancers have exploitable DDR pathways. Radionuclides emit α particles, β particles, or photons (either alone or in combination) during their radioactive decay. These emissions can damage DNA nucleotides or break strands. DNA strand breaks, especially double-strand breaks, are the most cytotoxic. If an irradiated cell is unable to coordinate its DDR pathways, it dies. Normal cells do this task well and do not die. Cancers deficient in one or more DDR pathways do not do this task well. Cancers are prone to die if overwhelmed by DNA damage. This might explain why external (conventional) radiotherapy will retain a palliative or immune system stimulatory role. But radiopharmaceuticals may have greater benefit in the long term. These radioactive drugs given by vein, injection, or ingestion irradiate distances that span one to 10 cells. Cancers absorbing radiation dose during radionuclide decay are overcome by unrepaird or lingering DNA damage. As these radioactive drugs induce more and more DNA damage, they stress missing or survival-dependent DDR pathways. This promotes cancer cell death. Finding human tumor genetic lesions sensitized to lethal radionuclide effects is desired. Radionuclides coadministered with targeted drugs or conjugated to tumor-specific antibodies are appealing given the probable wide therapeutic index (Table 1).

This article brings attention to an unappreciated monotherapy benefit for radionuclides in patients with ovarian cancer. Epithelial ovarian cancer harbors defective BRCA1 and BRCA2 in 22% of patients. Assuming that the proportion of defective BRCA1 and BRCA2 cancers existed over the prior period of radionuclide clinical development, there may be clues from prior evidence of radionuclide treatment efficacy that can be re-explored for patients.

### Ovarian Cancer Radiopharmaceutical Therapy Trial Examples

One historical approach tested in epithelial ovarian cancer treatment involved intraperitoneal instillation of chromic phosphate suspension ($^{32}$P, β− emitter). Its rationale followed logic that ovarian cancers spread early and multisite. Initial surgery might be incomplete, leaving occult residual peritoneal surface disease. Molecular characterization of tumors was impossible then. $^{32}$P suspension was given by intraperitoneal fenestrated catheter. It was thought to coat all peritoneal surfaces after carefully choreographed four-direction rolls. These 10-minute rolls repeated over a 2-hour period aided $^{32}$P coverage, as loculated pockets of peritoneal ascites blocked access to disease or concentrated $^{32}$P in pools contributing to toxicity. Several prospective randomized trials of $^{32}$P in epithelial ovarian cancer are summarized next.

### TABLE 1. Physical Properties of Select Radionuclides for the Treatment of Patients

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-Life</th>
<th>Decay Mode</th>
<th>Energy (MeV)</th>
<th>Prior Anticancer Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{32}$P</td>
<td>14.3 days</td>
<td>β−</td>
<td>1.70</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>$^{67}$Cu</td>
<td>2.6 days</td>
<td>β−</td>
<td>0.58</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>$^{89}$Sr</td>
<td>50.5 days</td>
<td>β−</td>
<td>1.49</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>$^{90}$Y</td>
<td>2.7 days</td>
<td>β−</td>
<td>2.28</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>$^{111}$In</td>
<td>2.8 days</td>
<td>EC</td>
<td>0.17, 0.25 gamma rays</td>
<td>Lymphoma</td>
</tr>
<tr>
<td>$^{131}$I</td>
<td>8.0 days</td>
<td>β−</td>
<td>0.61</td>
<td>Thyroid</td>
</tr>
<tr>
<td>$^{153}$Sm</td>
<td>1.9 days</td>
<td>β−</td>
<td>0.81</td>
<td>Bone metastases</td>
</tr>
<tr>
<td>$^{198}$Hg</td>
<td>26.8 hours</td>
<td>β−</td>
<td>1.85</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>$^{177}$Lu</td>
<td>6.7 days</td>
<td>β−</td>
<td>0.50</td>
<td>Neuroendocrine</td>
</tr>
<tr>
<td>$^{188}$Re</td>
<td>17.0 hours</td>
<td>β−</td>
<td>2.12</td>
<td>Liver cancer</td>
</tr>
<tr>
<td>$^{198}$Au</td>
<td>2.7 days</td>
<td>β−</td>
<td>0.41</td>
<td>Solid Tumor</td>
</tr>
<tr>
<td>$^{211}$At</td>
<td>7.2 hours</td>
<td>EC, α</td>
<td>7.45</td>
<td>Investigational</td>
</tr>
<tr>
<td>$^{213}$Bi</td>
<td>45.6 minutes</td>
<td>β−, α</td>
<td>8.00</td>
<td>Leukemia</td>
</tr>
<tr>
<td>$^{223}$Ra</td>
<td>11.4 days</td>
<td>β−, α</td>
<td>7.53</td>
<td>Prostate bone metastases</td>
</tr>
<tr>
<td>$^{227}$Th</td>
<td>18.7 days</td>
<td>α</td>
<td>6.00</td>
<td>Visceral metastases</td>
</tr>
</tbody>
</table>

Abbreviations: α, alpha particle (two protons, two neutrons); β, beta particle (one electron); EC, electron capture.
(limited to the ovaries) or stage 2 (limited to the pelvis) ovarian disease. The trial showed that about two-thirds of all \(^{32}\)P-treated patients had no side effects (18 of 68 [26%] had abdominal pain); four patients (6%) underwent exploratory surgery for non-disease-related bowel obstruction. Melphalan-treated patients experienced myelosuppression (74%), with 20% classified as severe. The single dose of \(^{32}\)P was as effective as 12-cycle melphalan, including rate of relapse (19% vs. 19%), 5-year progression-free survival (80% vs. 80%, \(p = .87\)), and 5-year overall survival (78% vs. 81%, \(p = .48\)).

A follow-up phase III trial (1986–1994) by the same investigators randomized postsurgical \(^{32}\)P or cisplatin-cyclophosphamide treatment.\(^{15}\) One hundred ten women were allocated to a single intraperitoneal \(^{32}\)P (15 mCi) dose. One hundred nineteen women were assigned to three-cycle cisplatin (100 mg m\(^{-2}\)) plus cyclophosphamide (1 g kg\(^{-1}\)) every 21 days. Women had stage 1 or 2 ovarian disease. Side effects from \(^{32}\)P were uncommon. There was a 4% rate of gastrointestinal toxicity. Three patients sustained ischogenic bowel perforations from catheter placement. In the other trial arm, toxicity was more frequent. Moderate to severe reductions in white blood cell (69%) or platelet (8%) count occurred. Gastrointestinal toxicity was 12%. \(^{32}\)P single dosing netted the same efficacy as three-cycle cyclophosphamide-cisplatin for all measures of efficacy. The 10-year cumulative rate of relapse was not significantly different (35% vs. 28%, \(p = .15\)). Both 5-year (78% vs. 82%) and 10-year (66% vs. 68%, \(p = .43\)) overall survival rates were similar statistically.

Another randomized trial from the Norwegian Radium Hospital (1982–1988) studied women with stage 1, 2, or 3 cancer (outside the pelvis or spread to retroperitoneal lymph nodes).\(^{14}\) Postsurgical treatment was either single intraperitoneal \(^{32}\)P (7–10 mCi) injection in 169 patients or six-cycle cisplatin (50 mg m\(^{-2}\)) infusion every 21 days. Women had stage 1 or 2 ovarian disease. The trial found toxicity to be uncommon in \(^{32}\)P-treated patients, with a single patient having a lung embolism (one of 136 [0.7%]). Surgery requiring nondisease bowel obstruction occurred in six patients (4%). Cisplatin treatment was stopped in 12 patients (7%) for not otherwise specified side effects. Two patients (1%) underwent surgery for nondisease bowel obstruction after cisplatin. The single dose of \(^{32}\)P was as successful as six-cycle cisplatin, as relapse rate (21% vs. 24%), 5-year progression-free survival (81% vs. 75%, \(p = .57\)), and overall survival (83% vs. 81%, \(p = .60\)) were essentially the same in statistical analyses.

To isolate the contribution of \(^{32}\)P in stage 3 ovarian cancer, another randomized trial was done after initial and second-look surgery.\(^{15}\) One group of 104 women received a single intraperitoneal \(^{32}\)P (15 mCi) dose. The other group of 98 women underwent no further treatment. On-trial toxicity was infrequent. Among \(^{32}\)P-treated patients, four patients (4%) experienced grade 3 or 4 hematologic side effects. Four (4%) had gastrointestinal side effects of the same grade. Three (3%) underwent surgery for nondisease bowel obstruction. In the group receiving no further treatment, four (4%) had hematologic side effects, two (2%) had gastrointestinal side effects, and one (1%) had surgery for a nondisease fistula. \(^{32}\)P was not superior to no further treatment of stage 3 patients. The rate of relapse (65% vs. 64%) was the same. The 5-year progression-free survival rate was 44%, compared with 34% (\(p = .27\)). The 5-year overall survival rate was 83%, compared with 81% (\(p = .60\)).

Within the limits of interpretation, these trials provide proof of concept that a radiopharmaceutical appropriately targeted in a disease-specific sense delivers benefit with a favorable safety profile in patients with ovarian cancer. The opportunity to reposition “old” radiopharmaceutical therapies to active treatment of patients takes advantage of possible exploitable DDRs in cancer. New agents such as antibody-radionuclide conjugates (e.g., antimesothelin antibody–\(^{225}\)Th conjugate; see Fig. 1) are of clinical interest for patients with early- and advanced-stage ovarian cancer. Adequately powered radiopharmaceutical therapy trials are of critical clinical importance now.

### Radiopharmaceutical Clinical Development

NCI takes in investigational agents for sponsored, collaborative clinical development through one mechanism, the NCI Experimental Therapeutics (NExT) program.\(^{16}\) Agent applications to NExT undergo a rigorous two-stage review. The first-level review is carried out by nonfederal clinician scientists per a special emphasis panel. The second-level review occurs by CTEP clinician scientists and cancer biologists. Agent applications scoring well submit additional “just-in-time” information to assist assigned CTEP medical officers in structuring a project team. A project team is a scientific review group for evaluation of agent scientific and clinical merit. Project teams involve interested clinician scientists, translational scientists, clinical pharmacologists, and cancer biologists. CTEP solicits membership to a project team. Once competed, applicants undergo two-stage review at CTEP. The first level involves the medical officers; the second level occurs with leadership. Afterward, project teams convene to discuss agent-specific science, pharmacology, and clinical performance to craft mature clinical development projects or trials multiple in number. CTEP monitors project team progress carefully. Active monitoring includes correspondences from investigators, medical officer reports, teleconferences, and other information. At its conclusion, project team work must be presented for approval to an investigational drug steering committee made up from a different set of nonfederal clinician scientists and cancer biologists. Final administrative reviews are conducted, and approval documents are sent to successful project team investigators. Trials often activate in the CTEP Experimental Therapeutics Clinical Trial Network, an integrated phase I and phase II program for the early clinical evaluation of innovative cancer treatments among select member NCI cancer centers with early drug development interest and capacity.\(^{17}\)

As an example of the NExT process, a radiopharmaceutical therapy in clinical development is \(^{223}\)Ra. Here, the drug substance is \(^{223}\)Ra dichloride. Modes of \(^{223}\)Ra decay involve both...
alpha particle (\(\alpha\), a helium ion containing two protons and two neutrons) and beta particle (\(\beta\), meaning one electron) emission. The total energy emitted by \(^{223}\text{Ra}\) and its daughters is 28.2 MeV, with alpha particles contributing 95.3% of this energy. Alpha particles can split cancer cell DNA to form a double-strand break. If unrepaird, the break may be lethal to the cancer cell. Initial clinical success of \(^{223}\text{Ra}\) in men with metastatic prostate cancer prompted interest in further evaluation of its broader clinical utility.\(^{18}\) CTEP has recently started a \(^{223}\text{Ra}\) and olaparib combination trial in a similar patient population via protocol 10096 (NCT03317382). A successful NEXT application for \(^{223}\text{Ra}\) has led to a project team. Solicited membership includes CTEP clinical researchers, radiopharmaceutical experts, and NCI Radiation Research Program investigators. Goals for the team include (1) selecting new tumor types for study and (2) monotherapy or combination trials for conduct in the Experimental Therapeutics Clinical Trial Network.

**PROGRAMMATIC COLLABORATION FOR RADIOPHARMACEUTICAL DEVELOPMENT**

NCI uses programmatic collaboration for two-stage appraisal of radiopharmaceutical NEXT applicants. The first stage involves joint discussion between CTEP and the Radiation Research Program.\(^{18}\) This level of review assesses any gaps in preclinical or clinical science much deeper than the simple resolve to jointly develop a radiopharmaceutical therapy. The second stage covers wider input from CTEP reviewers, such as provision of radiopharmaceutical handling, appropriate investigator registration and record keeping, and logistics of agent forecasting, acquisition, and inventory management. Successful applicants follow one of two clinical development paths. One is the solicited project team path for multiple trials discussed above. The other is an unsolicited path that requests a single trial supported by CTEP resources. Either path is subject to final administrative review and approval. Depending on design, trials may activate in the Experimental Therapeutics Clinical Trial Network or in the CTEP National Clinical Trials Network, a consolidated network of five cooperative groups responsible for late phase clinical evaluation of cancer treatments across a diverse multisite panel of American and Canadian cancer centers.\(^{20}\)

A relevant case of programmatic collaboration is the Radiation Research Program radiopharmaceutical therapy working group. This initiative provides a focused forum for federal and nonfederal clinician scientists and cancer biologists to freely discuss triumphs and barriers in radioactive drug development. Discussion offers opportunities to fast-track discovery and to boost return on prior investigative ventures such as from Small Business Innovation Research. NCI and its community of radiation oncology investigators are well positioned to enter into a radiopharmaceutical era of drug development over the next two decades. A suggested actionable agent list is provided in Table 1. Other cutting-edge ideas such as targeted antibody-radiopharmaceutical conjugates are a high priority.

**RADIOPHARMACEUTICAL INFRASTRUCTURE NEEDS**

NCI’s investment in radiopharmaceutical scientific review, management, monitoring, and other forms of vital infrastructure is key to creating innovative trials and to promoting full clinical development. NCI should consider investments in forward-thinking plans for radiopharmaceutical clinical research. And it is a good time to make those investments, after awarding 19 Small Business Innovation Research radiopharmaceutical development phase grants.

The NCI desires collaborative research planning and cost sharing with commercial suppliers to finance the desired radiopharmaceutical infrastructure and studies. More nonfederal spending would be welcome, but NCI is willing to take the lead in this area because the amount of assistance it would receive under any new nonfederal initiative remains unclear. One-off radiopharmaceutical therapy trials seem to omit many important areas of research, such as absorbed radiation dose dosimetry or pharmacokinetics.

The NCI should consider addressing unmet infrastructure needs now for several reasons. The investment should improve efficient, safe, and cost-effective study of radiopharmaceutical therapies, now and in the future. The first need is expert evaluation by physicians experienced in radiation oncology at initial NEXT program applicant triage. By leveraging existing scientific review capabilities in CTEP and the Radiation Research Program, early go or no-go decisions could be made without new resource allocation. This could boost overall operational efficiency in the clinical trial enterprise. A second need is to support a coordinated radiopharmaceutical dosimetry development team. Such a team would be charged with creating a radiopharmaceutical dosimetry development plan to be reviewed by a NCI radiation expert review committee. NCI often uses its contractors to administratively support these types of tasks. Additional funding may need to be allocated for the additional workload. NCI is in a strong position to provide infrastructure building. NCI’s clinical trial enterprise already has clinical monitoring and regulatory elements in user-friendly Web-based formats. Well-targeted infrastructure builds for radiopharmaceutical shipping and handling, investigator registration, commercial supplier–NCI interfaces for inventory tracking, and new electronic trial case report forms ensure workflow that can be relied upon in the near term and the long term.

**RADIOPHARMACEUTICAL DOSIMETRY**

Radiation dosimetry in health care means the quantified measure of ionizing radiation dose absorbed by the human body. Radionuclides given by vein, injection, or ingestion irradiate cancerous and normal tissue until excreted or decayed. The radiation dose absorbed over time is an integral of biologic decay (excretion) and radioactive decay, or the committed dose. To measure deposited radiation dose in patients, two parameters are needed. First, a volumetric scan of the patient must be done. Computed tomography and magnetic resonance imaging fit this need. Either modality permits radionuclide targeting and any at-risk anatomy to
be contoured for three-dimensional anatomic volume calculation. A volumetric scan of the radionuclide distributed in the patient must be captured. This second volume can be determined in two ways. A pretherapy scan can be done using a trace amount of the radionuclide to give the apparent volume of distribution (or the volume necessary to contain the total amount of an administered radionuclide at the same concentration that it is observed in the blood). Or a post-therapy scan of fully distributed radionuclide can be obtained for the volume of interest. Mathematical algorithms compiling spatial anatomy and radionuclide deposition determine patient committed dose. These algorithms assume that administered radionuclides are not reinjected, reingested, or reinhaled after body elimination.

From this vantage point, radiopharmaceutical therapies are amenable to pharmacokinetic analyses. Early-phase drug development trials explore drug absorption, distribution, and elimination by blood tests. Most radionuclides can undergo the same by whole-body nuclear imaging studies. This is an attractive property for clinical development plans. As phase I trials typically home in on toxicity, radiopharmaceutical pharmacokinetics should inform safe dose and schedule, with the least number of patients exposed to serious or life-threatening adverse events. Connecting administered activity and administered intensity (i.e., the frequency of radionuclide dosing) is important to the final safety profile of the study radiopharmaceutical agent. CTEP encourages such an approach for drug development. It is reasonable to apply this notion to radiopharmaceutical therapy development as well.

Conceptual obstacles in dosimetry remain. It is clear that, when effort is expended, radiopharmaceutical absorbed dose to a patient can be calculated. One challenge is relative biologic effectiveness. In radiobiology, effectiveness is in part the ratio of cell kill from one type of ionizing radiation to photon-based ionizing radiation given the same absorbed energy (Table 1). Beta particles, gamma rays, and x-rays all have a weighting factor (WR [formerly Q]) of 1. Alpha particles can have a WR as high as 20. The higher the WR, the greater a cell’s DNA is damaged. Another part of effectiveness is bioavailability. Bioavailability here means the proportion of a radionuclide drug that enters the circulation when introduced into the body and therefore capable of an antitumor effect. Radiopharmaceutical therapies that target tumors have a higher relative biologic effectiveness than those that do not. A second challenge is relative uncertainty in therapeutic index. The traditional phase I trial investigation describes adverse events associated with agent administration, targeting a toxicity rate of 33% or less. It does not necessarily suit the development of radiopharmaceutical therapies in monotherapy or combinations when an agent’s committed dose is uncharacterized. Perhaps a more informative role for radiopharmaceutical dosimetry is to help point out warning of unforeseen toxicity. This may help reduce patient risk, identify acceptable toxicity, and uncover vulnerable patient populations. And last, there is the contemporary test of calculating committed dose across time independent images without or with deformable registration.

A “good” early-phase radiopharmaceutical development study includes dosimetry. Careful dosimetry guides study design by reducing the number of trial subjects exposed to serious toxicity. It provides context for starting dose and schedule, with the smallest number of trial subjects exposed to subtherapeutic doses. It aids in describing therapeutic intent in a disease-specific manner. For all these reasons, radiopharmaceutical dosimetry adds value in a radionuclide clinical development program.

CONCLUSION

Radiotherapy retains a central role in the era of personalized medicine because of exploitable DDRs in cancer. Radiopharmaceutical therapies introduce new ways to add clinical benefit to patients. Novel biotechnology for systemic radionuclide therapy opens new paths of clinical investigation. Programmatic collaboration at the NCI facilitates radiopharmaceutical discovery. This enhances its return on investment and pushes brand-new therapies to patients. Having a commitment to radiopharmaceutical dosimetry should reduce morbidity and enhance survival for patients.

References


Moving From Mutation to Actionability

Ilaria Colombo, MD, Katherine C. Kurnit, MD, Shannon N. Westin, MD, and Amit M. Oza, MD

OVERVIEW

The diffusion of high-throughput next-generation sequencing technologies has sustained massive parallel sequencing of tumor tissue providing a deep insight into tumor biology and advancement of personalized medicine. A substantial number of targeted agents have been investigated in gynecologic cancer and some have received U.S. Food and Drug Administration approval, like PARP inhibitors in ovarian cancer, bevacizumab in ovarian and cervical cancers, and pembrolizumab in microsatellite-unstable or mismatch repair–deficient endometrial cancer. To improve effectiveness of targeted therapy, identification of predictive biomarkers able to guide the selection of the correct drug for the correct patient is crucial. Different limitations must be addressed to favor a more rapid implementation of a genotyping approach in treatment selection, such as the possibility to easily assess tumor heterogeneity and clonal evolution along the disease trajectory and the need for innovative trial designs like adaptive or basket trials incorporating molecular features as selection criteria. A deep dive into the genomic features of exceptional responders may also favor better understanding of tumor biology, mechanism of action of a specific target agent, and identification or predictive biomarkers for subsequent tailored studies.

THE ROLE OF TARGETED THERAPY IN GYNECOLOGIC CANCERS

Over the last decade, remarkable advances have been achieved in the “omics” technologies, (genomic, proteomic, transcriptomic) enabling rapid DNA and RNA sequencing and changing the paradigm of cancer treatment that is now moving from a “one-size-fits-all” strategy to personalized medicine. Identification of predictive biomarkers has become a touchstone for drug development with the aim of matching patients to a specific targeted treatment that is no longer based on disease site or histologic subtype but on the specific actionable molecular aberration. The advent of high-throughput sequencing technologies had led to identification of an incredibly high number of somatic mutations with the added challenge of distinguishing “driver” from “passenger” mutations. The fundamental principle of precision medicine lies in the possibility to directly or indirectly act on these mutations, identify predictive biomarkers, and improve treatment effectiveness by matching the right treatment to the right patient. Following the characterization of molecular landscapes of ovarian, endometrial, and cervical cancers by The Cancer Genome Atlas (TCGA), many different targeted therapies have been investigated and some approved for the treatment of gynecologic cancers. However, efficacy, type of actionability, and presence of biomarkers to guide patient selection are different between agents (Fig. 1).

Driver Mutations and Direct Actionability

PARP inhibitors. Repair of DNA damage is necessary to maintain genomic stability, promote cell survival, and replication. Base excision repair pathways are involved in the repair of single strand DNA breaks where PARP plays a role. Inhibition of PARP leads to accumulation of double-stranded DNA breaks normally repaired by homologous recombination (error-free pathway) or by nonhomologous end joining (error-prone pathway). Different enzymes are recruited to repair double-stranded DNA breaks, such as BRCA1, BRCA2, and other homologous recombination proteins. Germline or somatic mutations in BRCA1/2 or defects in other homologous recombination repair system genes (e.g., EMSY, RAD51, ATM, ATR, Fanconi Anemia, BARD1, BRIP1, PALB2, CHEK2, PTEN, MRE11A and others), are known as homologous recombination deficiency (HRD) and observed in 50% to 60% of high-grade serous ovarian cancer (HGSOC) cases. The presence of HRD sensitizes cancer cells to PARP inhibitors (PARPi) through “synthetic lethality.” Evidence from phase II and III trials confirmed the role of PARPi for the treatment of relapsed platinum-sensitive and platinum-resistant ovarian cancer (OC) and as maintenance treatment of platinum-sensitive relapse after response to platinum-based chemotherapy. Direct comparison between PARPi (olaparib, niraparib, and rucaparib) is challenging given differences in selection criteria (BRCA1/2-mutated only versus inclusion of wild-type BRCA1/2), HRD definition, study design, inclusion or exclusion of patients with residual bulky
disease, or abnormal CA125 level in maintenance clinical trials. Although the magnitude of PARPi benefit is higher in patients carrying BRCA mutations or HRD, these molecular features cannot be completely used as predictive biomarkers given that benefit is still observed when mutations are not present. Improvements in response rate (RR) and progression-free survival (PFS) have been observed in homologous recombination proficient and in unselected (“all comers”) populations. The ARIEL-2 (NCT01891344) and ARIEL-3 (NCT01968213) trials investigated a tumor-based molecular signature of HRD capable of predicting rucaparib activity beyond germline or somatic BRCA mutations. As a consequence of HRD, genomic scars accumulate and may be measured as an extension of genomic loss of heterozygosity (LOH). Although LOH score (high vs. low) can define which subgroups of patients are more likely to benefit from rucaparib, it cannot be exclusively used as a biomarker of response given that improvement in PFS, although arguably clinically significant, has been observed in patients with BRCA wild-type and LOH-low tumors.

**PI3K/AKT/mTOR inhibitors.** The PI3K/AKT/mTOR is the most frequently mutated or dysregulated pathway in endometrial cancer (EC) and a highly “druggable” target. Yet, after nearly 20 years of preclinical and clinical studies, a predictive biomarker or signature to target this pathway with PI3Kinase or mTOR inhibitors remains elusive for clinical practice. Different mTOR inhibitors have shown signs of activity in phase II trials with RR 4% to 24% but with significant toxicities. Activation of redundant pathways restoring PI3K activity has been reported as one of the most relevant mechanisms of resistance and led to investigation of combination strategies involving multitarget treatment (pan-PI3K, AKT, and PI3K-mTORC dual inhibitors) to overcome primary or acquired resistance. However, the risk of significant toxicities is of particular concern in patients with EC known to be frail and with multiple comorbidities. Thus, targeting this pathway is challenging given pitfalls such as patient selection, toxicity management, and biomarker identification. All these aspects must be considered in designing clinical trials with the aim of bringing these agents into clinical practice where they are urgently needed to improve patient outcomes. Moreover, deep genome tumor analyses in patients with exceptional response to PI3K/AKT/mTOR inhibitors may elucidate underlying mechanisms of action and support predictive biomarker discovery.

### Driver Mutations and Indirect Actionability

**Immune checkpoint inhibitors.** Immune checkpoint inhibitors (anti–PD-1/PD-L1) are under investigation in gynecologic cancers, but despite different targeted therapies that have been investigated for the treatment of gynecologic malignancies, precision, sensitivity, and specificity of predictive biomarkers to guide treatment selection remain a challenge. Although the presence of BRCA mutation or homologous recombination deficiency is a biomarker of the magnitude of benefit, they cannot, as yet, be used to exclude patients from PARP inhibitor treatment, given clinical benefit is also observed in patients with wild-type BRCA or homologous recombination proficient tumors. As data further support the benefit of molecularly matched therapies, there are an increasing number of molecularly driven clinical trials on a variety scales. Thus, the optimal timing, utility, and logistics of NGS in gynecologic malignancies are expected to evolve. Gynecologic cancers include a number of distinct tumor types with a unique pattern of alterations and challenge NGS gene panel design. There is an urgent need to consider changing trial design to encompass all gynecologic patients into biomarker-based, basket-type clinical trials.

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### PRACTICAL APPLICATIONS

- Identification of driver and actionable mutations in tumor tissue allows the development of precision medicine, with the aim to match the drug to patient according the specific molecular profile.
- Despite different targeted therapies that have been investigated for the treatment of gynecologic malignancies, precision, sensitivity, and specificity of predictive biomarkers to guide treatment selection remain a challenge.
- Although the presence of BRCA mutation or homologous recombination deficiency is a biomarker of the magnitude of benefit, they cannot, as yet, be used to exclude patients from PARP inhibitor treatment, given clinical benefit is also observed in patients with wild-type BRCA or homologous recombination proficient tumors.
- As data further support the benefit of molecularly matched therapies, there are an increasing number of molecularly driven clinical trials on a variety scales. Thus, the optimal timing, utility, and logistics of NGS in gynecologic malignancies are expected to evolve.
- Gynecologic cancers include a number of distinct tumor types with a unique pattern of alterations and challenge NGS gene panel design. There is an urgent need to consider changing trial design to encompass all gynecologic patients into biomarker-based, basket-type clinical trials.

**FIGURE 1. Efficacy, Type of Actionability, and Presence of Biomarkers in Gynecologic Cancers**
cancers and are of particular interest in specific subtypes of endometrial cancer with high rates of somatic mutations: the ultramutated group harboring mutations of polymerase epsilon (POLE) and the hypermutated group characterized by microsatellite instability–high (MSI-high) or deficient mismatch repair system. The POLE and the MSI groups, accounting for 10% and 25% of all recurrent endometrial cancers respectively, have a higher level of neoantigens and tumor-infiltrating lymphocytes with high expression of PD-1/PD-L1, supporting the rationale to investigate immunotherapy. A phase II study (NCT01876511) investigating pembrolizumab in mismatch repair–deficient solid tumors regardless of disease site, enrolled 86 patients including 15 patients with endometrial cancer. Objective radiologic responses have been observed in 53% (46/86) of patients, with 21% (18) achieving a complete response and a 2-year PFS of 53%. In the endometrial cohort, three patients (20%) had complete response, five (33%) partial response, and three stable disease (20%) as best response. In the phase IB KEYNOTE 028 (NCT02054806) trial assessing pembrolizumab in PD-L1–positive advanced/metastatic solid tumors, 23 patients with EC were evaluable for response. At the time of data cut-off, three patients (13%) had a partial response and three (13%) stable disease for 24.6 weeks. Among the three patients with a partial response, one had POLE mutation, one non-MSI high tumor, and one unknown MSI status. Although clinical benefit seems higher in patients with higher mutation burden, objective responses have been also reported in non-MSI endometrial cancer. Thus, further investigation is needed to identify predictive biomarkers and to define the role of PD-L1 expression to guide patient selection. In the cohort of advanced/recurrent cervical cancer (10 patients), an RR of 17% was reported.

In advanced ovarian cancer, anti–PD-1/PD-L1 therapies have shown a smaller magnitude of benefit with lower RRs (0%–15%) likely due to low mutation burden and tumor immunogenicity. However, early signs of activity have been observed in specific subtypes commonly resistant to chemotherapy, such as clear cell, warranting further investigation.

No Actionable Mutations

**Angiogenesis.** Angiogenesis is an hallmark process of cancer growth and progression and plays an important role in ovarian cancer. Different agents have been investigated, and, among these, the anti-VEGF monoclonal antibody bevacizumab has shown to increase PFS and overall survival (OS) in different settings of ovarian cancer treatment. When used in the first-line setting, PFS is increased by 4 months as observed in the GOG 218 trial (NCT00262847) and the median OS by 9 months in the high-risk population (stage IV, inoperable, or suboptimally debulked stage III) of ICON7 (NCT00483782). In the recurrent setting, the GOG213 (NCT00565851) trial showed an improvement of 3.4 months in PFS and 5 months in OS when bevacizumab has been added to carboplatin and paclitaxel (or gemcitabine) for platinum-sensitive recurrence. An improvement of 4 months in PFS has been also observed when bevacizumab is added to carboplatin and gemcitabine for the treatment of platinum-sensitive recurrence (OCEANS trial, NCT00434642) and of 3.4 months in the platinum-resistant setting when added to weekly paclitaxel, liposomal doxorubicin, or topotecan (AURELIA trial, NCT00976911). Despite the fact that high levels of VEGF have been associated with poor outcomes in ovarian cancer, no predictive biomarkers have been identified. This limits the ability to select patients who are most likely going to benefit from bevacizumab and to spare nonresponders from unnecessary toxicity, which would allow for a more efficient and cost-effective use of this agent. A retrospective biomarker analysis of GOG-218 reported possible association between high density of vascular endothelial cells that usually express VEGF-receptor and high-tumor VEGF-A with patient outcomes. A retrospective analysis of ICON7 pretreatment plasma has identified a signature of three biomarkers (mesothelin, fms-like tyrosine kinase 4, and α1-acid glycoprotein) that combined with CA125 can predict benefit. However, prospective studies are warranted to confirm the predictive role of these biomarkers and their applicability in clinical practice.

Importantly in recurrent/advanced cervical cancer, bevacizumab improved OS, irrespective of any biomarker. This led to U.S. Food and Drug Administration (FDA) approval of the combination and a National Cancer Institute clinical alert. Antiangiogenic agents like sunitinib, bevacizumab, aflibercept, sorafenib, and cediranib have been tested in endometrial cancer in phase II trials showing RRs of 5% to 18% and a PFS rate at 6 months of 30% to 40%. However, given the lack of phase III trials and absence of biomarkers to identify patients more likely to benefit, no antiangiogenic agents have been approved for the treatment of endometrial cancer. Further studies assessing angiogenesis inhibitors in combination with chemotherapy or other targeted agents and focused on biomarker discovery are warranted.

**NGS GENE PANELS**

**NGS Gene Panels on Actionable Mutations**

With the advent of NGS, molecular assessment of all tumor types has evolved rapidly. Whereas assessments were previously limited to individual genes in the era of Sanger sequencing, NGS subsequently allowed for rapid assessment of many genes simultaneously. However, unlike many other tumor types, gynecologic tumors have had relatively few genotype-specific targeted therapeutics approved by the FDA. Aside from *BRCA* mutations for several PARPi and MSI-high for pembrolizumab, no other drug has achieved a biomarker-specific FDA approval in gynecologic malignancies. This is true even for gynecologic tumors containing mutations in genes associated with approved targeted therapies in other tumor types (e.g., *BRAF* V600E). As more data support the benefit of molecularly matched therapies, there is an increasing number of molecularly driven clinical trials. This is true on both a smaller scale with single or multi-institution trials, as well as on a national level with National Cancer Institute and ASCO efforts. Thus, the optimal timing,
utility, and logistics of NGS in gynecologic malignancies are expected to evolve.

Currently, the majority of “standard-of-care” molecular testing is performed using commercially available gene panels. Although these panels have indications for use in all solid tumors, only two have approval for gynecologic malignancies: FoundationFocus CDX BRCA (Foundation Medicine) and myChoice HRD (Myriad). Both of these tests are approved for ovarian cancer only and used primarily for the consideration of PARPi therapy.46,47 FoundationOne CDX was recently approved as an NGS gene panel test for all solid tumors and includes genomic signatures for tumor mutation burden and MSI assessments. However, this panel is relatively unique in that it is also approved as a companion diagnostic for FDA-approved therapies in five tumor types: ovarian cancer, non–small cell lung cancer, melanoma, breast cancer, and colorectal cancer. Additionally, other non-FDA–approved options for molecular assessment of gynecologic malignancies exist, including Caris Molecular Intelligence (Caris Life Sciences), Tumor Blueprint (The Clearity Foundation), TumorNext-HRD and TumorNext-Lynch (Ambry Genetics), and Oncomine Comprehensive Assay (Thermo Fisher Scientific). Other common techniques including immunohistochemistry (e.g., for PTEN loss assessment) and fluorescence in situ hybridization (e.g., for HER2 amplification assessment) continue to be used on a hospital-by-hospital basis. However, newer molecular characterization techniques including RNAseq and reverse phase protein array have also begun to emerge for clinical use.48,49

**Challenges for Designing NGS Gene Panels**

Gynecologic cancers include a number of distinct tumor types with a unique pattern of alterations. The majority of ovarian cancers are epithelial, and the majority of epithelial ovarian cancers are HGSOC. Although the most frequent mutation in HGSOC is in TP53, therapies targeting this alteration are still in preclinical or early-phase clinical trials.50 Currently, the most clinically relevant alterations in epithelial ovarian cancers are those associated with HRD. In TCGA’s molecular characterization of ovarian cancers, approximately 50% of tumors were found to have alterations, which led to nonproficient homologous recombination DNA repair. Interestingly, although most of these homologous recombination defects were in BRCA1/2, almost 15% were in other genes, suggesting that somatic (including epigenetic) and other germline alterations may be relevant to HRD-related targeted therapeutics.51 Cohort studies and clinical trials have already shown that patients with ovarian cancer demonstrating HRD but without a germline BRCA mutation, behave similarly to patients with germline BRCA mutations in terms of clinical outcomes and treatment response.52-55 Furthermore, recent data from niraparib and rucaparib show improved response to PARPi in tumors with evidence of HRD based on aberrations other than mutations, such as LOH.22,56 Thus, identification of patients with HRD and ongoing development of relevant therapeutics will be critical for patients with HGSOC.

Other epithelial ovarian cancer subtypes have an array of potentially actionable mutations. A large proportion of low-grade serous ovarian cancers have KRAS and BRAF mutations, as well as high expression of estrogen and progesterone receptors.57,58 Endometrioid ovarian cancers have high rates of PI3K pathway alterations as well less frequent BRCA, ARID1A, and CTNNB1 mutations.59 Similarly, clear cell ovarian cancers have high rates of PI3K pathway alterations and a higher frequency of ARID1A mutations compared with HGSOC.60,61 Mucinous ovarian cancers have frequent KRAS and BRAF mutations as well as HER2 amplification.62,63 In adult granulosa cell tumors, FOXL2 mutations have been found, and DICER1 mutations in several other nonepithelial ovarian cancers,64,65 but their clinical relevance is presently unclear as fewer biomarker-driven clinical trials have been completed in patients with these cancers.

For endometrial cancer, the molecular landscape has been well-described, but clinical success with targeted therapies has been modest. TCGA’s study of endometrial cancer demonstrated notable alterations in PTEN, PIK3CA, PIK3R1, ARID1A, KRAS, and CTNNB1 in tumors with endometrioid histology.4 In fact, it is more common for endometrioid tumors to have at least one molecular abnormality than to be completely wild-type. The high number of mutations, and specifically the propensity for PI3K/AKT pathway alterations, has been supported by other smaller, single-institution studies as well.66-69 TCGA also demonstrated high rates of TP53 mutations in the endometrial cancers that were predominantly of serous histology as well a proportion of high-grade endometrioid tumors.4 Interestingly, studies have also demonstrated HER2 overexpression and amplification in uterine serous carcinomas.70-72 From a tumor mutational burden standpoint, two subsets of patients characterized as having hypermutated (mostly MSI-high) and ultramutated (POLE mutants) disease were also identified in endometrial cancer.4 A subset of endometrial cancers with high tumor mutational burden has been identified in multiple other studies and is increasingly of clinical interest.73,74

For HPV-related gynecologic cancers, including cervical, vaginal, and vulvar cancers, many novel therapeutics have focused on the HPV aspect of these tumors and less on the molecular landscape. However, molecular characterization of these tumor types has increased in recent years, including a TCGA analysis of cervical cancers published in 2017.75 Interestingly, TCGA’s analysis identified several cervical cancer subsets. Although most were defined by HPV-related characteristics, there was a small subset that appeared more similar to endometrial cancer. This endometrial-like group demonstrated a significantly higher proportion of KRAS, ARID1A, and PTEN mutations than the rest of the cervical cancers assessed. Additionally, the majority of these tumors showed an alteration in either the PI3K/MAPK or the TGF-beta signaling pathways. High frequencies of the PI3K and MAPK pathways have similarly been shown in other smaller studies.76,77 However, the finding of a subset of tumors with ERBB3 mutations was relatively novel and suggests a new targetable pathway for these patients.75
The targetable alterations of vulvar and vaginal cancers are vastly unknown. A recent NGS molecular assessment of vulvar cancers demonstrated mutations in the PI3K/MAPK pathway, as well as TP53 mutations and a small number of ERBB4 mutations.\textsuperscript{78} Of note, significantly more alterations were seen when immunohistochemistry was used compared with NGS, underscoring one of the complexities of identifying predictive biomarkers for novel therapeutics. Unfortunately, these data also suggest that we may not be able to easily extrapolate between tumors of different primary sites even when the tumorigenesis mechanism is thought to be similar.

**Clinical Relevance of NGS Gene Panels**

One of the ongoing debates for molecular testing that is not limited to gynecologic malignancies, is related to the optimal timing of such testing. Currently, most molecular testing for gynecologic malignancies occurs in the recurrent setting. This is in large part due to a lack of FDA-approved targeted therapies available in the upfront setting. At this point, most molecular testing in gynecologic malignancies is done with the goal of finding appropriate biomarker-driven clinical trials for patients with disease that have failed upfront therapy. Less often, clinicians may use therapies off-label.\textsuperscript{79} This may be particularly relevant to rare tumors that have no available tumor-specific clinical trials. In addition to the lack of standard-of-care options currently associated with molecular testing, concern regarding tumoral molecular evolution over time may make tumor testing less valuable if other therapies are anticipated prior to the initiation of a targeted agent.

However, as the field of precision oncology evolves, it is quite plausible that targeted agents will move to the primary setting as well. As they achieve approvals for gynecologic cancers in the recurrent setting, clinical trials assessing targeted therapies in the upfront setting will become less controversial. As seen in treatment of non–small cell lung cancer, which has evolved from cytotoxic chemotherapy based on histologic subtypes into parallel treatment algorithms based on its molecular subgroups,\textsuperscript{80} gynecologic malignancies may ultimately move toward a more molecularly based treatment approach. Although ALK-positive non–small cell lung cancer is only present 3% to 5% of the time, the benefit of crizotinib was so overwhelming in this patient population that it is now clinically recommended to test all patients with non–small cell lung cancer at diagnosis.\textsuperscript{80,81} To allow similar successes to be achieved for patients with gynecologic cancer in the future, clinical trials must be carefully designed to study the specific patient populations of greatest relevance, while capitalizing on the relatively small numbers of patients who are diagnosed with gynecologic malignancies each year.\textsuperscript{82}

One possible solution may be with the use of basket trials (i.e., multiple tumor types with a single biomarker). Currently, several large National Cancer Institute (NCI) basket trials such as NCI-MATCH (Molecular Analysis for Therapy Choice) and NCI-MPACT are ongoing across a variety of solid tumor types, including gynecologic malignancies. Other smaller single- and multi-institution basket trials are ongoing. The initial results from the MyPathway Study were recently published and demonstrated promising responses in multiple tumor types harboring relevant biomarkers for several targeted therapies.\textsuperscript{83} Although most patients did not have gynecologic malignancies, seven patients with uterine cancer and 14 patients with ovarian cancer were enrolled. Although none of the seven patients with uterine cancer and only one of the eight patients with ovarian cancer achieved a clinical response to HER2-directed therapy, two of the four patients with *BRAF* V600E ovarian cancer achieved a partial response to vemurafenib.\textsuperscript{83} Although these results may be somewhat disappointing, they do help guide where future efforts might be most efficiently directed. In addition, ASCO’s Targeted Agent and Profiling Utilization Registry (TAPUR) is ongoing and will help capture patients being treated off-label in a formal tracking system.

These large tumor-agnostic trials have the potential to provide a mechanism to identify biomarker-driven targeted therapies for gynecologic cancers while taking advantage of the relatively higher numbers of patients with other common tumor types such as breast, colorectal, and lung cancers. This type of trial design recently helped result in an FDA-approval of pembrolizumab for MSI-high tumors.\textsuperscript{20} Although endometrial cancers did not comprise the majority of tumors enrolled on the trials, patients with this disease (as well as other patients with other gynecologic cancers) can now receive pembrolizumab as standard of care if they are found to be MSI-high.

Basket trials have also been shown to be feasible when limited to patients with gynecologic cancer. Several studies targeting the PI3K/AKT pathway in gynecologic malignancies harboring relevant mutations have been successfully completed,\textsuperscript{84–86} and other similar trials are currently ongoing. Although it could be argued that some of the gynecologic malignancies have no more in common with each other than with other solid tumor types (e.g., vaginal cancer and ovarian cancer), from a logistics standpoint, basket trials of gynecologic malignancies make practical sense as many of these patients are being seen by oncology groups who only treat gynecologic cancer. As the numbers of known biomarkers and targeted therapies continue to grow, optimizing the efficiency of clinical trials for patients with gynecologic cancer will be critical to the development of future targeted therapies for these patients.

**Molecular Profiling and Targeted Therapy Pitfalls**

In gynecologic cancers as in other malignancies, several limitations and controversies must be addressed to promote integration of molecular medicine into standard practice and clinical trials.

**Tissue accessibility.** Commonly, most of the genomic tests are performed at one time point on archival tissue to spare patients from invasive biopsy. Tumors are characterized by temporal and spatial heterogeneity with progressive evolution of molecular aberrations along the disease trajectory and by the presence of clonal evolution in the different sites...
of a metastatic disease. Therefore, new dynamic strategies capable of avoiding multiple tumor biopsies that are time-consuming, costly, and with potential risks for the patients have been investigated. The application of targeted NGS on circulating cell-free DNA (cfDNA) has been used to overcome these limitations. cfDNA is released into the blood stream upon cell death and can be isolated and interrogated for molecular aberrations. These liquid biopsies are easily performed (through blood, paracentesis, and thoracentesis), less invasive, repeatable during disease evolution, and can provide information on residual disease, disease burden, tumor heterogeneity, resistance mutations, clonal evolution, and be used as potential predictive biomarker for response to treatment. cfDNA can be identified in blood or liquid-based Pap smears in patients with early-stage disease, representing a promising tool for screening in high-risk populations.

Cost and complexity of genotype-based health care. The implementation of precision medicine in clinical decision-making and in trial design is increasing the cost and complexity of health care and clinical research in oncology. Rapid improvement in the detection of genomic alterations linked to cancer susceptibility and the widespread use of multigene hereditary panels has also led to increased identification of families at higher risk for cancer (e.g., germline BRCA mutation, Lynch syndrome, Li-Fraumeni syndrome). Genetic counseling and discussion about potential risk reduction strategies (surgical or pharmacologic) and prevention must be incorporated in the treatment plan. This has to be proactively offered to patients but also to first-degree family members, and adequate access to genetic testing needs to be promoted in underserved and high-risk communities.

A growing number of targeted therapies are receiving approval by health authorities with substantial costs for the treatment itself and for the management of related toxicities, sometimes with only limited improvement of patient outcomes. Efforts to develop biomarkers to better select patients more likely to benefit from a specific targeted agent are necessary to sustain a cost-effective strategy able to match the treatment with the genetic make-up of the disease. Although NGS technologies are now more affordable and accessible, the high complexity of results requires bioinformatics support, clinician education, and molecular tumor board discussion to correctly interpret molecular data and adequately integrate them into patient care.

Drug development and clinical trial design. The advent of precision medicine and the growing number of new targeted agents are changing the paradigm of drug development. To date, only a few strong genomic biomarkers are actionable with approved standard targeted agents (e.g., ALK fusion and EGFR mutation in non–small cell lung cancer, HER2 amplification in breast and gastric cancers, BRAF V600 mutation in melanoma, KRAS mutation in colorectal cancer). Some aspects are relevant to improve drug development: (1) deep “omics” analyses of exceptional responders to understand the underlying mechanism of action and identify a potential genomic signature to guide future development; (2) implementation of genotype selection in early-phase clinical trials; and (3) promotion of new trial designs (e.g., adaptive strategy or basket trials) to increase the chance to observe signs of clinical activity in early-phase studies and favor a more rapid process of drug approval, especially when facing rare tumors. Approximately 30% to 40% of patients with gynecologic cancers are diagnosed with a rare subtype of cancer (< 6 cases per 100,000 per year). When disease-specific trials are challenged by the low tumor incidence, need for international collaborations, lack of funding, slow accrual, and absence of standard treatment, molecularly matched trials may favor discovery of urgently needed effective agents. Furthermore, despite the large number of targeted agents tested in clinical trials, only a minority reach the market and become available for treatment. It is not uncommon to have patients with unexpected dramatic or long-lasting responses to these novel therapies after previous lines of treatment. A deep investigation into the tumor biology of these tumors may help in understanding the mechanism of action of the drug and identify potential genomic aberrations responsible for the exceptional response that can be potentially used as a predictive biomarker and further investigated in genotype-based clinical trials.

References


COLOMBO ET AL


HEAD AND NECK CANCER
Major Changes in Head and Neck Staging for 2018

William Lydiatt, MD, EMBA, FACS, Brian O’Sullivan, MD, FRCPC, FRCSI, and Snehal Patel, MD, FRCS

OVERVIEW

Oncologists should be aware of three major modifications and additions to staging head and neck cancer that became effective in 2018. Oral cavity cancers have the addition of depth of invasion; oropharyngeal cancers (OPCs) are now distinguished by the immunohistochemical stain, p16, into those that are associated with high-risk human papillomavirus and those that are not; and all sites except nasopharyngeal carcinoma and high-risk human papillomavirus OPC will now include the important parameter of extranodal extension. The rationale and emerging data supporting these changes are discussed in this article and the accompanying oral presentation at the 2018 ASCO Annual Meeting.

Staging cancers is an important tool for oncologists to define the natural history of disease, help to predict prognosis, support the surveillance community to facilitate cancer control at the registry level, and compare clinic trials across locales and is essential as a stratification factor for clinical and translational research. Periodic updates to staging systems are necessary to accurately reflect emerging data, differentiate novel diseases, and better capture the real-world experiences of clinicians and patients. The eighth edition of the AJCC Cancer Staging Manual (TNM classification from the American Joint Committee on Cancer [AJCC] and the Union for International Cancer Control [UICC]) reflects these principles. The AJCC head and neck task force, working with their partners in the UICC, sought to maintain harmony between the two dominant world systems for cancer staging as they introduced incremental staging changes, which took effect January 1, 2018. Three major changes to head and neck staging will be highlighted in this article, including adding depth of invasion to oral cavity cancer, introducing novel pathologic and clinical staging system for high-risk human papillomavirus–positive (HPV+)–associated oropharyngeal cancer (OPC), and the incorporation of extranodal extension (ENE) in nodal characterization in high-risk HPV–negative (HPV–) and non-nasopharyngeal carcinoma. This article and the accompanying oral presentation given at the 2018 ASCO Annual Meeting will highlight the AJCC/UICC staging changes, present the rationale for the changes, and provide preliminary data that have emerged.

ANATOMY

A common misperception in the lay press is the conflation of the oropharynx with the oral cavity. Because each of the changes in staging discussed in this article are site dependent, a brief word on this distinction is important. Many press reports describe the high-risk HPV association with oral cancer. Although there are associations with HPV in the oral cavity, they are uncommon, and it is not apparent at this time what implication these have on the etiology or outcome of these cancers. What is clear is that HPV-related cancer of the oropharynx, determined by the surrogate immunohistochemical marker p16, is one of the most common cancers in the head and neck in the western world and is associated with a substantially better outcome for tumors in the OPC (specifically, cancers arising in the palatine and lingual tonsils). Educating patients about the difference is important for them to understand the impact of HPV in the etiology of their disease when it occurs in the oropharynx; it is also important for practitioners to appreciate why depth of invasion affects staging in the oral cavity.

Anatomic specifics for the TNM were slightly adjusted for the oral cavity in the eighth edition to better reflect the somewhat differing cause of lip and oral cavity cancers and transitional embryology of the vermillion of the lip relative to either the skin or the oral mucosa. The vermilion border of the lip is now staged by using the chapter on skin cancer to either the skin or the oral mucosa. The vermilion border extends to the anterior tonsillar pillars, the circumvallate papilla and the junction of the hard and soft palate and includes the buccal mucosa, wet mucosal surfaces of the lips, dental alveolar structures, floor of mouth, oral tongue, and hard palate. The oropharynx is defined by its boundary with the oral cavity anteriorly, the extension of the soft palate to the posterior pharyngeal wall posteriorly-superiorly, and the plane of the hyoid inferiorly. The oropharynx includes the palatine tonsils, the base of the tongue.
and lingual tonsils, and the lateral and posterior pharyngeal walls between the soft palate and hyoid.

DEPTH OF INVASION

To improve the ability to differentiate oral cavity cancers with smaller horizontal size but more aggressive behavior, depth of invasion (DOI) has been added to oral cavity T characterization. The previous parameter of extrinsic muscle invasion was removed because it was hard for pathologists to define and lacked specificity. This refinement reflects decades of data indicating that depth is a negative prognosticator in cancers of the tongue, buccal mucosa, and floor of mouth in particular. This is similar to other cancers, such as melanoma and uterine cervix. Initial data by Spiro and colleagues suggested that 3 mm of invasion substantially increases the risk for nodal metastases and thus portended a worse prognosis.6 Subsequent work has found depths of 4 or 5 mm as the important branch points, but all studies supported the idea that increasing depth of invasion augured a quantitatively worse prognosis.5–8 The large retrospective multi-institutional international study performed by Ebrahimi and colleagues also supported at least a 5-mm specitive multi-institutional international study performed by Ebrahimi and colleagues also supported the idea that increasing depth of invasion augured a quantitatively worse prognosis.5–8 The large retrospective multi-institutional international study performed by Ebrahimi and colleagues also supported at least a 5-mm increment, or greater for more advanced T categories, along with the traditional T character of horizontal size.9

Assessing DOI in a large data set was important in refining the staging criteria. However, many cancer registry data sets lack details on DOI. Therefore, only data sets with this parameter could be used to develop the staging paradigm. The data that were used to analyze outcomes in patients with oral cancer came from a combined prospective data set of two North American tertiary cancer care centers (Memorial Sloan Kettering Cancer Center [MSKCC] and Princess Margaret Hospital [PMH]) that share common workup and treatment strategies (Table 1). DOI of the primary tumor was used to modify T criteria for patients with oral cancer largely on the basis of the Ebrahimi study. Figure 1 shows the prognostic outcomes based on the new T criteria proposed in the eighth edition. In particular, the enhanced hazard consistency and discrimination among T1 and T2 tumors with increasing DOI was compelling, although this was also evident for T3 lesions.

The difference between DOI and tumor thickness requires special attention. Although in many cases these will be very similar, the data reported are not always consistently one or the other. DOI was chosen over thickness to avoid stage migration of the more indolent-acting cancers, which present as thick exophytic cancers but with minimal invasion. Determination of DOI may be difficult at times and may not always be readily apparent, just as determining the clinical size of a lymph node or pharyngeal or oral cavity tumor is not exact. However, clinicians for years have been assessing tumors and estimating their size by using meticulous assessment and measurement. This will be the case with depth. The clinician should try to ignore the exophytic portion of the tumor and assess the portion that invades below the surface. The clinician should use the standard rule of staging and err on the side of the lower appropriate stage.

Recent publications have supported the improved hazard discrimination in oral cavity staging with the addition of DOI. Matos and colleagues retrospectively investigated nearly 300 patients and determined that by using the pT category of the eighth edition, 22.9% of patients were upstaged with DOI.10 These patients had a higher recurrence rate and a lower disease-specific survival compared with rates seen with use of the seventh-edition TNM criteria, suggesting an improved predictive capacity.

TABLE 1. Characteristics of Patients With Oral Cavity Cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Combined</th>
<th>MSKCC</th>
<th>PMH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>1,792</td>
<td>1,119</td>
<td>673</td>
</tr>
<tr>
<td>Median follow-up (range), months</td>
<td>44.30 (0.03–307.75)</td>
<td>51.02 (0.13–307.75)</td>
<td>38.23 (0.03–197.61)</td>
</tr>
<tr>
<td>Median age (range), years</td>
<td>60 (15–96)</td>
<td>60 (16–96)</td>
<td>61 (15–89)</td>
</tr>
<tr>
<td>Men, no. of patients</td>
<td>1,064 (59)</td>
<td>642 (57)</td>
<td>422 (63)</td>
</tr>
</tbody>
</table>

Abbreviations: MSKCC, Memorial Sloan Kettering Cancer Center; PMH, Princess Margaret Hospital.

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opinions have now converged on the principle that a novel staging system was needed to properly depict the character and prognosis of this new disease, which contrasts with smoking-related/HPV-unrelated (HPV−) OPC from which the traditional TNM classification was derived. Through use of the seventh edition TNM classification, most patients with high-risk HPV+ OPC were discovering that they have stage IV disease, but the reality was that their prognosis rivals that of patients with the most curable cancers. This was alarming for many patients and clinicians first facing their cancer diagnosis and might perpetuate a philosophy that traditional intensified treatments are always needed, which is under challenge.

Over a relatively recent period since the official recognition of the viral cause of this disease by the World Health Organization in 2007, evidence emerged that the behavior of HPV-related OPC is unsuited to the seventh edition staging system. In particular, investigators at The University of Texas MD Anderson Cancer Center noted a change in survival in the most recent decade for OPC with unknown HPV status. It is now recognized that HPV causation was emerging as the dominant form of the disease during this time, compared with an earlier period (1955–2004), when the disease was predominantly caused by alcohol and smoking. This survival advantage had unexpected stage specificity with unusually favorable outcome for stage III and IV disease in the recent period that disrupted the prognostic ability of the entire stage classification. Similarly, Straetmans and colleagues observed that lymph nodal involvement and extent of nodal disease seemed not to be associated with reliable prognostic ability. Subsequently, Keane and colleagues pointed out a changing prognostic significance from the later 1990s until 2008 in the Surveillance, Epidemiology, and End Results (SEER) database for oropharyngeal squamous cell carcinoma without knowledge of HPV status. They observed an emerging pattern for both the T classification and

**FIGURE 1. Overall Survival Based on T Criteria**

![Overall Survival Graph](image)

<table>
<thead>
<tr>
<th># of pts</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>429</td>
<td>376</td>
<td>313</td>
<td>262</td>
</tr>
<tr>
<td>T2</td>
<td>564</td>
<td>460</td>
<td>345</td>
<td>276</td>
</tr>
<tr>
<td>T3</td>
<td>377</td>
<td>286</td>
<td>206</td>
<td>180</td>
</tr>
<tr>
<td>T4</td>
<td>222</td>
<td>179</td>
<td>191</td>
<td>121</td>
</tr>
</tbody>
</table>

Abbreviations: AJCC, American Joint Committee on Cancer; Cum, cumulative. Reproduced with permission from AJCC Manual on Staging, eighth edition.
N classification in which essentially the T4 category was the only consistent T component with an appreciably higher hazard ratio for survival compared with T1 in the most recent decade. They also noted a surprising evolution in pattern of reduction of hazard ratio for survival for all seventh edition N2 subcategories compared with N0 disease.\textsuperscript{14}

**Clinical TNM**

Huang and colleagues at the Princess Margaret Hospital undertook a “discovery” study using 810 patients with OPC treated almost exclusively with radiotherapy with or without chemotherapy.\textsuperscript{15} They showed that patients with high-risk HPV+ OPC (573 patients) did not demonstrate prognostic discrimination by using the seventh edition TNM; this was particularly the case for stage IV disease, with no significant separation of survival curves from stage I to IV (p = .56).\textsuperscript{15} In contrast, HPV− disease (273 patients) showed acceptable performance from stage I to IV (p = .04). The study used several statistical assessments, including recursive partitioning (RPA) and adjusted hazard ratios (AHRs) to derive two classifications using the existing T and N categories of the seventh edition TNM for the HPV+ cohort.\textsuperscript{15} Both classifications were compared with the seventh edition TNM using modified criteria from Groome and colleagues,\textsuperscript{16} which evaluated performance according to five established criteria: (1) hazard consistency, to assess the similarity of overall survival (OS) for subgroups defined by T and N within each stage group; (2) hazard discrimination, to evaluate the differences in OS between stage groups to assess how equally they were spaced; (3) explained variance, to calculate the percentage of OS variation explained by the stage groupings; (4) sample size balance, to examine the difference in sample sizes across stage groups; and (5) likelihood difference, to evaluate the difference in goodness of fit between the models.

The RPA-based TNM stage grouping (stage I/II/III: T1−3N0−N2b/T1−3N2c/T4 or N3, with M1 as stage IV) was proposed for HPV-related OPC as a result of substantially improved survival prediction compared with the seventh edition TNM. The AHR model also yielded a valid classification, but RPA stage demonstrated better survival prediction at this phase of derivation. Interestingly, within the PMH cohort from Huang and colleagues, 56% of patients classified as stage III or IV according to seventh edition TNM criteria would migrate to stage I. Huang and colleagues’ RPA

### TABLE 2. Regional Lymph Nodes Clinical Category Criteria (cN) Except Nasopharyngeal and High-Risk HPV+ OPC

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node &gt; 3 cm but not &gt; 6 cm in greatest dimension and ENE−; or metastases in multiple ipsilateral lymph nodes, none &gt; 6 cm in greatest dimension and ENE−; or in bilateral or contralateral lymph nodes, none &gt; 6 cm in greatest dimension, ENE−</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in single ipsilateral node &gt; 3 cm but not &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral nodes, none &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node more than 6 cm in greatest dimension and ENE−; or metastasis in a single ipsilateral node ENE+; or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in a single ipsilateral node ENE+ or multiple ipsilateral, contralateral or bilateral nodes any with ENE+</td>
</tr>
</tbody>
</table>

**Abbreviations:** ENE, extranodal extension; HPV, human papillomavirus; OPC, oropharyngeal cancer.

**Notes:**

**TABLE 3. Regional Lymph Node Pathologic Category Criteria (pN) Except Nasopharyngeal and High-Risk HPV+ OPC**

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in a single ipsilateral lymph node, ≤ 3 cm in greatest dimension and ENE+; or &gt; 3 cm but not &gt; 6 cm in greatest dimension and ENE−; or metastases in multiple ipsilateral lymph nodes, none &gt; 6 cm in greatest dimension and ENE−; or metastases in a single ipsilateral lymph node &gt; 3 cm but not &gt; 6 cm in greatest dimension, ENE+</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in single ipsilateral node ≤ 3 cm in greatest dimension and ENE+ or a single ipsilateral node &gt; 3 cm but not &gt; 6 cm in greatest dimension, ENE−</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral nodes, none &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE− or metastasis in a single ipsilateral node &gt; 3 cm in greatest dimension and ENE+ or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node &gt; 6 cm in greatest dimension and ENE−</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in a single ipsilateral node &gt; 3 cm in greatest dimension and ENE+ or multiple ipsilateral, contralateral, or bilateral nodes any with ENE+</td>
</tr>
</tbody>
</table>

**Abbreviations:** ENE, extranodal extension; HPV, human papillomavirus; OPC, oropharyngeal cancer.

A designation of U or L may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE classification should be recorded as ENE− or ENE+.

**Notes:**
classification was subsequently validated pragmatically in an external administrative data set of the National Cancer Database (NCDB) by Horne and colleagues in an analysis of 8,803 patients with HPV+ OPC which included 9% treated with surgery alone.17

After the discovery study by Huang and colleagues, a confirmatory study was undertaken to refine the classification by using training and validation statistical maneuvers to rederive the models with a new external data set from a multi-institutional cohort. The new confirmatory derivation study was undertaken by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) and derived a classification for high-risk HPV+ OPC, which was subsequently adopted by the UICC and AJCC for the eighth edition TNM to more appropriately depict the character and prognosis of the disease.18

The ICON-S study was an international collaboration evaluating approximately 2,600 patients with OPC, of whom 1,907 had high-risk HPV and were from seven institutions across Europe and North America. Like the original discovery study at PMH, ICON-S initially re-examined the existing seventh edition TNM, which performed appropriately for HPV− patients (696 patients), with a monotonic OS reduction according to seventh edition staging. Five-year OS rates for seventh edition stage I, II, III, IVA, and IVB were 76% (95% CI, 61%–95%), 68% (95% CI, 56%–81%), 53% (95% CI, 44%–64%), 45% (95% CI, 40%–50%), and 34% (95% CI, 25%–48%), respectively. However, among high-risk HPV+ cases, the seventh edition TNM fared very poorly, with OS rates inseparable for stage I, II, III, and IVA (5-year OS rates: I, 88% [95% CI, 74%–100%]; II, 82% [95% CI, 71%–95%]; III, 84% [95% CI, 79%–89%]; IVA, 81% [95% CI, 79%–83%]; p = .25) but lower in stage IVB (5-year OS: 60% [95% CI, 53%–68%]; p < .001), essentially driven by N3 disease in this stage subset. Furthermore, 5-year OS did not differ in patients with high-risk HPV+ OPC among N0 (80%; 95% CI, 73%–87%), N1–N2a (87%; 95% CI, 83%–90%), and N2b (83%; 95% CI, 80%–86%) subsets. As was performed by Huang and colleagues, ICON-S also explored RPA and AHR models. Both were again compared against, and proved to be superior to, seventh edition TNM. The AHR model was based on a multivariable Cox model calculated adjusted (age, smoking, and treatment) HRs for risk for death with various T–N combinations, considering minimal hazard difference, the ordinal order of T and N categories, and the sample size balance between new potential stage subgroups. Because instances of N1–N2b disease all behaved similarly, they were classified within a single N subcategory (N1), such as NPC, the other viral-related pharyngeal disease, nasopharyngeal carcinoma, whereas contralateral or bilateral neck disease (formerly N2c in the seventh edition) was reclassified as N2, and N3 remained unchanged from the seventh edition. The T categories behaved independently from T1 to T4, but there was no apparent subdivision within T4 and survival was identical between T4a and T4b. The eventual ICON-S stage classification was based on the AHR model, which had the better performance and the most practical TNM stage tabulation “grid.” The stage tabulation for the latter included stage I (comprising T1/T2 and N0/N1), stage II (composed of T3 and N2 disease), and stage III (made up from T4 and N3 disease). Stage IV disease

![FIGURE 2. Overall Survival in Lip and Oral Cavity Cancer Based on N Criteria That Incorporate Extranodal Extension as a Prognostic Factor](image-url)
was reserved for distant metastases (M1 disease), similar to many other non–head and neck cancers.

After the new ICON-S stage system was derived, meta-analysis was applied to evaluate the heterogeneity of the stage performance across different institutions. The meta-analysis used the generic inverse-variance methods and forest plots to assess heterogeneity across different institutions. Heterogeneity tests showed that the hazard ratio for ICON-S III versus II and II versus I were in the same direction (> 1.0 for higher stages) across all institutions, which supports the applicability of ICON-S classification across various jurisdictions. Of the ICON-S HPV+ data set, 48% of seventh edition TNM stage III–IV would migrate to eighth edition TNM stage I.

ICON-S was subsequently adopted for the eighth edition because it enhanced the UICC/AJCC TNM stratification into more valid groups compared with the seventh edition to facilitate patient counseling, cancer surveillance, and translational research and to optimize clinical trials design and outcome reporting. This is a prerequisite because all patients must be staged at the time of initial diagnosis before treatment is undertaken. Subsequently, several pragmatic external validation studies from single institution and administrative data have been undertaken with excellent monotonic decrements in survival from stage I to stage II to stage III with or without stage IV (when analyzed). Of interest, although primarily a report of surgical management with the prime goal of deriving a postsurgical TNM (pTNM) classification to accommodate the emerging strategy of endoscopic surgery, one report showed that the ICON-S classification (eighth edition clinical TNM) also performs in an exemplary manner for surgically treated patients. This underlines the utility of the clinical TNM classification as applied to the disease overall, irrespective of the management undertaken.

**FIGURE 3. N Criteria Validated by Using the Memorial Sloan Kettering Cancer Center–Princess Margaret Hospital Institutional Data Set**

Abbreviations: AJCC, American Joint Committee on Cancer; Cum, cumulative.

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Pathology-Based pTNM

Regarding the aforementioned study of surgically treated patients, Haughey and colleagues developed a pTNM staging that also uses three separate tiers of risk based on the existing primary tumor pT category classification (also without subdivision into T4a and T4b) combined with metastatic node count identified after neck node dissection. This recognizes recent advances in surgical management, predominantly using transoral techniques, and the need to guide and investigate postsurgical treatments. As in the case of clinical TNM mentioned, a discovery process was initially undertaken through a study (220 patients) at Washington University. This study challenged the existing premise that laterality and extracapsular lymph node spread were predominant risk factors in the transoral surgical case treated with postoperative adjuvant treatment. The findings were that a combination of AJCC/UICC pT classification and pathology-confirmed metastatic node count (four or fewer versus five or more) yielded three groups: stages I (pT1–T2, four or fewer nodes), II (pT1–T2, five or more nodes; pT3–T4, four or fewer nodes), and III (pT3–T4, five or more nodes), with incrementally worse prognosis. This was subsequently explored in a pragmatic multicenter study (equivalent to the derivation study of ICON-S) comprising 704 patients.

Abbreviations: AJCC, American Joint Committee on Cancer; Cum, cumulative.
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exclusively treated by transoral surgery in five centers in the United States or United Kingdom.\textsuperscript{19}

Subsequently, Zhan and colleagues reported an external validation study that used registry data (specifically the NCDB) on 3,745 patients treated with surgery from 2010 to 2014.\textsuperscript{26} They found excellent hazard discrimination and prognostication among stage I, II, and III for the eighth edition pTNM classification. On a cautionary note, however, Zhan and colleagues also observed that extranodal extension (ENE) was present in 41% of cases and that this attribute confers a subtle but significant negative effect on overall survival in this large patient sample (92% ENE\textsuperscript{−} vs. 85% ENE\textsuperscript{+}; p < .001). Furthermore, examination of the confirmatory derivation study from Haughey and colleagues also observed that extranodal extension (ENE) was present in 41% of cases and that this attribute confers a subtle but significant negative effect on overall survival in this large patient sample (92% ENE\textsuperscript{−} vs. 85% ENE\textsuperscript{+}; p < .001). Furthermore, examination of the confirmatory derivation study from Haughey and colleagues showed a trend in univariate analysis for worsening survival in the presence of pathologic evidence of extranodal disease (p = .06) and a significant detriment associated with contralateral lymph node involvement (formerly seventh edition N2c; p = .049). Notable also in this surgical series is the lower proportion of patient with N2c disease (7%; detected pathologically) compared with greater than 20% in the ICON-S study (all determined clinically). Whether this represents false-positive results clinically or a selection away from operating on bilateral disease is unknown. Multivariate analysis also indicated that both adjuvant radiotherapy and chemoradiotherapy appeared to confer survival advantage by using Cox regression.\textsuperscript{19}

In the end, a workable pathologic staging system now seems feasible to guide prognosis and adjuvant therapy decisions in surgically managed HPV– oropharyngeal squamous cell carcinoma and has been adopted for the pTNM eighth edition. It should facilitate refinement of clinical trial risk stratification, with the caveat that some aspects continue to merit close study in the future, including the presence and degree of extranodal extension and the degree of intensity of treatment that should be used in the presence of such adverse features.

\textbf{FIGURE 5. Overall Survival in Patients With Oral Cancer After Adjustment of Stage Groups (Memorial Sloan Kettering Cancer Center–Princess Margaret Hospital Data)}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure5}
\caption{Overall Survival in Patients With Oral Cancer After Adjustment of Stage Groups (Memorial Sloan Kettering Cancer Center–Princess Margaret Hospital Data)}
\end{figure}

\textit{Abbreviation: Cum, cumulative. Reproduced with permission from the AJCC Manual on Staging, eighth edition.}
Relevance of TNM Eighth Edition to Management

Importantly, determination of high-risk HPV status for the purposes of staging is undertaken through the use of the surrogate marker p16, determined by immunohistochemistry for overexpression of the tumor suppressor protein p16 (cyclin-dependent kinase 2A). Therefore, p16 staining must be performed on all OPCS for proper staging. p16 was chosen because of lower cost, widespread availability, and relative ease of interpretation as opposed to specific determination of high-risk HPV.

A new clinical classification for high-risk HPV+ OPC is now included in the eighth edition TNM that is relevant to cases treated with surgical or nonsurgical approaches. However, this classification reflects prognosis under the current treatment paradigm, in which many patients received intensified treatment, and concern remains about whether the excellent prognosis of high-risk HPV+ OPC would continue in all cases if intensity were reduced. Stage I does not necessarily imply limited treatment is required. Thus, practitioners must be mindful that the TNM classification is not a guideline for treatment but provides a framework for clinical research and treatment decision-making that must continue to acknowledge other important tumor factors (e.g., presence of extranodal extension), treatment factors (e.g., resection margin status, radiotherapy dose, mode of systemic treatment), and patient factors (e.g., age, performance status, and potentially a quantified assessment of smoking history). The only safe path to modify treatment will be from the results of properly designed clinical trials.

EXTRANODAL EXTENSION IN ALL HEAD AND NECK CANCER SITES EXCEPT NASOPHARYNGEAL CANCER AND HPV-ASSOCIATED P16+ OPC

Metastasis to the regional lymph nodes is the most powerful predictor of outcome in traditional (typically, tobacco-associated) head and neck cancers, and the status of the cervical nodes is therefore mandatory for prognostic prediction. Characteristics of metastatic nodes, such as the size of the node(s), the number of nodes involved, and laterality relative to the primary tumor, have always been accounted for in previous iterations of the AJCC/UICC staging system. However, ENE, which has long been known to be an important feature of nodal metastases in non–high-risk HPV+ tumors, was not used in previous editions of the staging system.

The eighth edition introduces ENE in the N category for both clinical and pathologic staging of tumors not associated with high-risk HPV (Tables 2 and 3).

Early or microscopic ENE can be identified only on pathologic examination but cannot be detected reliably on clinical examination or with any currently available imaging modality. The AJCC/UICC committee has therefore set a high bar for incorporating ENE into clinical staging so that only patients with unambiguous clinical evidence of ENE supported by, but not exclusive of, radiographic evidence should be designated ENE+. Clinical ENE requires unequivocal clinical signs of gross ENE, such as skin involvement or muscle invasion causing tethering or fixity of the nodal mass, or dysfunction of a cranial nerve, the brachial plexus, the sympathetic trunk, or the phrenic nerve, supported by strong radiographic evidence of ENE.

Pathologic ENE is defined as extension of metastatic carcinoma through the fibrous capsule of a lymph node into the surrounding connective tissue, regardless of the presence of stromal reaction. Tumor that stretches the capsule without breaching it does not constitute ENE. The extent of ENE is subcategorized as ENE_m (macroscopic gross ENE that is apparent to the pathologist’s naked eye or extends > 2 mm beyond the nodal capsule under the microscope, or a soft tissue deposit that has completely destroyed nodal architecture) or ENE_m (microscopic ENE that is restricted to ≤ 2 mm from the nodal capsule). These subcategories are recommended for data collection and are both considered as ENE+ for definition of pN.

These changes in N category were based on analysis from large data sets of oral cavity cancer, which is primarily treated surgically; thus, they allow incorporation of histopathologic features, such as ENE. The N categorization of HPV-negative–associated tumors was heavily influenced by oral cavity data from MSKCC and PMH discussed above based on the extrapolation that these tumors have clinical behavior similar to that of other tobacco-associated cancers of the larynx, hypopharynx, and HPV− OPC, as well as paranasal sinus, skin, and salivary gland malignancies. Revision of the N criteria was based on a preliminary analysis of ENE on a data set from the NCDB, including patients treated in 2010 to 2011 (Fig. 2). These results were then validated by using the MSKCC-PMH institutional data set (Fig. 3).

The interplay of the new T and N criteria for stage grouping was then examined by using the MSKCC-PMH data set according to seventh edition AJCC/UICC criteria (Fig. 4) because NCDB data did not have information on DOI of the primary tumor. The seventh edition groupings did not discriminate between stages II and III, and this is likely due to the redistribution of prognostic weight of DOI and relatively lower impact of low-volume metastatic nodal disease. The stage groups were therefore appropriately adjusted to take into account the effect of these newer prognostic factors; the MSKCC-PMH data were reanalyzed and demonstrated improved discrimination of stage groups (Fig. 5).

A limitation of these analyses is that similar cancer registry data were not available on DOI of the primary tumor and ENE. Stage groupings for the eighth edition will therefore remain unchanged for now, pending validation of these results on cancer registry data sets in the future.

As an aide memoir for practitioners for what might seem a confusing “new” classification, it may be helpful to recall the following: In the earliest strata of the pN categories, only N1 is affected uniquely, and here the presence of ENE in a single ipsilateral lymph node less than 3 cm in maximum dimension migrates that category to N2a; pN2 nodes will migrate to pN3b, whereas all other N categories remain the same as seventh edition TNM in the absence of EN. The presence of cENE migrates them all uniformly to the new adverse subcategory of cN3b. A new subcategory of N3a is created to maintain attention to the rare instance of a node greater than 6 cm where ENE is not identified.
CONCLUSION
Staging of head and neck cancers has undergone a major revision in three key areas. DOI now is used to better discriminate oral cavity cancers, high-risk HPV+ p16+ OPC is now staged by using a novel system with much better predictive capability, and nodal disease is further refined by whether ENE is present. It is important for the oncologist to understand these modifications for accurate data collection and patient stratification so that new treatment paradigms can be better determined through clinical trials.

References
4. Lydiatt WM, Patel SG, O’Sullivan B, et al. Head and neck cancers—major revision in three key areas. DOI now is used to better discriminate oral cavity cancers, high-risk HPV+ p16+ OPC is now staged by using a novel system with much better predictive capability, and nodal disease is further refined by whether ENE is present. It is important for the oncologist to understand these modifications for accurate data collection and patient stratification so that new treatment paradigms can be better determined through clinical trials.

Personalizing Postoperative Treatment of Head and Neck Cancers

Ellie Maghami, MD, FACS, Shlomo A. Koyfman, MD, and Jared Weiss, MD

OVERVIEW

Head and neck cancer (HNC) treatment is a complex multidisciplinary undertaking. Although overtreatment can result in functional and cosmetic defects, undertreatment can result in cancer recurrence. Surgery and chemoradiotherapy are both accepted standards for the curative intent treatment of locally advanced mucosal squamous cell carcinoma of the head and neck, but are often prioritized differently depending on the site of tumor origin (e.g., oral cavity/sinonasal vs. oropharynx/larynx), tumor burden, tumor biology, quality-life considerations, and patient preference. Regardless of modalities chosen, failure to cure remains a considerable problem in locally advanced disease. For patients treated with primary surgery, high-risk pathologic features portend higher recurrence rates, and adjuvant therapy can reduce these rates and improve outcomes. This report details which tumor- and nodal-related factors are indications for adjuvant therapy, examines the impact of tumor HPV status on adjuvant treatment paradigms, and considers which systemic therapies should be used for which patients when trimodality therapy is indicated.

For early-stage HNCs, single-modality therapy with surgery or radiation therapy (RT) was demonstrated highly effective for local control by multiple prospective trials. In T1 to T2 cancers of the digestive tract, a local control rate of 80% to 90% was reported with either surgery or radiation alone.1 For T3 to T4 tumors, single-modality treatment led to unacceptable higher failure rates. In 1996, Mishra et al2 reported on 140 patients with T3 to T4 N0-2b buccal squamous cell carcinoma randomly assigned to receive surgery with or without postoperative adjuvant RT. Local recurrence was significantly higher in patients undergoing surgery alone (25% vs. 10%), and 3-year disease-free survival (DFS) was significantly higher in those receiving adjuvant RT (68% vs. 38%).3 In the preadjuvant therapy era, locoregional recurrence occurred in 30% of patients and distant recurrence in 25%.4 Surgery and postoperative RT became the accepted standard for advanced-stage HNC. A prospective randomized trial reported on prognostic pathologic variables for postoperative RT and the importance of both timing of postoperative RT initiation and duration of postoperative RT completion in advanced-stage disease.4

The National Comprehensive Cancer Network enlists the following poor risk indicators in the postoperative setting: positive margin, extranodal extension (ENE), lymphovascular invasion (LVI), perineural invasion (PNI), advanced T stage (T3-T4), high grade, advanced N stage (N2 to N3), and involved nodes in levels IV and V as indicators for addition of postoperative adjuvant therapy.5 Other prognosticators frequently discussed in multidisciplinary tumor boards include presence of worst pattern of invasion (WPOI),6 recurrent disease, nodal yield, and nodal ratio in neck dissection specimen.7-10 In cases of oropharyngeal squamous cell carcinoma (OPC), tumor p16 status (a surrogate marker for HPV) and patient’s smoking history are considered,11 with the caveat that the National Comprehensive Cancer Network does not currently endorse treatment modification based on these factors outside of carefully designed clinical trials. Interestingly, 25% of patients with HNC registered in the National Cancer Database did not receive adjuvant therapy as recommended according to National Comprehensive Cancer Network guidelines.12 Patient and hospital-based factors may have been involved.

Although the National Comprehensive Cancer Network provides a general framework for management, knowledge of clinical trials and investigations that have led to these recommendations is critical to the more sophisticated day-to-day nuanced approach to HNC treatment. This report examines prognosticators historically important for the addition of postoperative adjuvant therapy; it reports the state of the evidence currently available for the growing population of HPV-mediated OPC (HPVOPC) managed with up-front surgery; and finally, it examines indications, benefits, and toxicity derived from the addition of chemotherapy to radiation in the adjuvant setting. In a recent publication...
surgical resection followed by low-dose or standard-dose intensity-modulated RT in resectable p16+ locally advanced oropharyngeal cancers, a negative margin was defined as 3 mm or greater, a close tumor margin as less than 3 mm from ink, and a positive margin as tumor present at the ink. This definition is being harmonized among several clinical trials and is often helpful in recommending adjuvant therapy for a margin of less than 3 mm.

Another important consideration in assessing margins is the specimen from which margins are assessed. There are considerable differences in how margins are assessed across different institutions. In general, "specimen-driven" assessment of margins is preferable to "defect-driven" evaluation of margins. In specimen-driven analysis of margins, the pathologists examine the main resected specimen and then sections the specimen perpendicularly through the tumor and measures the distance between the leading tumor edge and the surgeon's cut in millimeters. In defect-driven sampling, the surgeon provides strips of tissue taken from the remaining wound bed for margin analysis. For spatially complex resections, a combined specimen-driven and defect-driven analysis of margins may be necessary to achieve satisfactory clearance as important landmarks on the main specimen may be lost due to tissue contraction and relative slippage of tissues against one another. Retrospective studies have shown that achieving negative margins off the primary specimen (i.e., specimen-driven margins) leads to lower risks of recurrence in oral cavity cancer surgery compared with negative margins assessed from the tumor bed (i.e., defect-driven margins). Tumor-bed margins were shown not to be adequately sensitive predictors of margin status on the main resection specimen. Reliance on tumor-bed margins for decisions regarding adjuvant treatment may lead to undertreatment. Similarly, margins that require repeated frozen-section attempts for microscopic clearance carry a higher risk of recurrence, exceeding 25%. In transoral robotic surgery for OPC, the need to take two or greater margins to achieve complete resection was recently shown to carry an increased risk of locoregional recurrence and death due to disease. Adjuvant RT can be considered in this circumstance. For OPC, intraoperative and final positive margins are shown to be significantly more likely for base of tongue tumors than tonsil tumors (35.3% vs. 12.4%, respectively; p = .002) and (19.6% vs. 4.5%, respectively, p = .004) respectively. With transoral laser microsurgery technique, a tumor may be removed in multiple pieces, and margin assessment becomes highly operator dependent and complex, requiring careful tumor mapping, orientation, processing, and reporting by both surgeon and pathologist. To date, there are difference of opinions and substantial biases as to what constitutes a clear, close, or positive margin. In a large report of transoral surgery for HNC, a margin was generally considered clear unless microscopic tumor was seen to touch ink on the final permanent slides.

In deciding adequacy of margins of resection, pattern of invasion (POI) at the tumor-host interface should be considered. POI at the deep tumor margin was found to be...
a strong prognosticator of local control for early-stage oral and glottic cancers.\textsuperscript{5,20} POI types 1 through 4 were originally defined by Bryne et al: type 1 with tumor invasion in a broad pushing manner, type 2 with pushing "fingers" or separate large tumor islands, type 3 with invasive tumor islands of greater than 15 cells per island, and type 4 with even smaller tumor islands of 15 or fewer cells down to even isolated single invasive cells.\textsuperscript{20} Brandwein-Gensler added a new type 5 pattern of invasion in 2005, which describes a dispersed pattern of tumor invasion with distance of 1 mm or greater of normal tissue between tumor satellites of any size.\textsuperscript{6} In the study and reporting of tumor resection slides, the highest POI score is deemed the WPOI.\textsuperscript{6} WPOI-5 is a validated marker of poor LRC in early-stage oral squamous cell cancer (OCSCC) and predicted 42\% locoregional recurrence supporting adjuvant therapy.\textsuperscript{21} In another report on early-stage OCSCC, an infiltrative growth pattern was associated with a WPOI of greater than 1 mm of the circumference of a nerve and has been associated with increased lymph node metastasis and worse DSS and OS in OCSCC.\textsuperscript{29,30} In a study of early OCSCC, PNI predicted a worse 5-year DSS compared with patients presenting without PNI (76\% vs. \textgreater{} 92\%; \( p < .003 \)). \textsuperscript{31} In addition, PNI predicted regional lymph node metastasis on multivariate analysis (55\% vs. 21\%; \( p = .017 \)). Elective neck dissection in patients with early OCSCC with PNI was found to significantly reduce the rate of neck recurrence from 85.7\% to 16.2\% (\( p = .001 \)) and is indicated for patients with cN0 disease with PNI-positive tumors for improving DSS as well as neck control. In another study of low-risk patients who were treated by surgery alone, including neck dissection, the 5-year DSS rates were almost the same in those with PNI-positive and -negative tumors (92.0\% vs. 92.9\%; \( p = .9104 \)).\textsuperscript{32} The authors concluded that low-risk patients PNI-positive disease who undergo neck dissection do not need postoperative adjuvant therapy, because the residual risk from PNI is minimal. The use of adjuvant RT for OCSCC with isolated PNI remains controversial and is not universally recommended, as there is no conclusive evidence that RT improves local control in the absence of other adverse pathologic features.\textsuperscript{29}

LVI has been associated with worse local control, LRC, and OS.\textsuperscript{33,34} LVI in 180 patients with node-negative OCSCC (85\% were T1 to T2) treated with up-front surgery was associated with worse LRC and OS.\textsuperscript{33} Three-year LRC rates were 38.8\% (95\% CI, 22.8\%–54.6\%) for patients with LVI compared with 81.9\% (95\% CI, 74.4\%–87.4\%) in those without LVI. Three-year OS rates were 71.3\% (95\% CI, 53.2\%–83.4\%) in patients with LVI compared with 90.3\% (95\% CI, 83.8\%–94.3\%) in those without LVI. As such, the authors recommend adjuvant radiation in patients with node-negative disease with LVI.

**NODAL FACTORS WARRANTING POSTOPERATIVE ADJUVANT THERAPY**

Lymph node involvement was established as an indication for adjuvant RT decades ago, as surgery alone in these patients is historically associated with high risks of recurrence.\textsuperscript{35} Recent large database studies have confirmed this observation in modern times.\textsuperscript{36} The number of involved metastatic nodes and the overall nodal yield in neck dissection specimen both confer prognostic significance. In OCC, each positive node confers an additional 40\% relative risk of mortality, up to four nodes.\textsuperscript{9} In addition, the number of nodes harvested, regardless of whether they are cancerous, impacts survival. As a quality metric, some studies suggest that harvesting less than 18 nodes in a neck dissection leads to worsened survival,\textsuperscript{8} whereas others suggest that survival improves with even more thorough neck dissections up to 35 nodes.\textsuperscript{9} As such, inadequate lymph node dissections in patients with a relatively high risk of microscopic nodal involvement should be considered for adjuvant RT. There are a number of studies indicating lymph node ratio, the number of involved nodes over the number of nodes removed, as another relevant prognosticator for OS in patients treated with up-front surgery.\textsuperscript{7} Conversely, patients with a single involved node in an otherwise adequately dissected neck have excellent outcomes
with surgery alone, and RT can be deferred in these patients.37 These data underscore the rationale for surgical acumen and diligence in both staging and therapeutic neck dissections.

ENE has been shown in many prospective and retrospective studies to be one of the most powerful predictors of outcome in node-positive HNCs.28 In a large single-institution experience of transoral robotic surgery for OPC, 61% of node-positive cases had evidence for ENE, and presence of ENE was a considerable predictor of distant metastasis and OS.13 Both clinical and pathologic ENE appear in the eighth edition of the American Joint Committee on Cancer Cancer Staging Manual for nonvivally mediated cancers. Clinical ENE is marked by tissue invasion and fixation (skin, dermis, and muscle) and/or nerve infiltration by nodes involved with tumor. For ENE, the negative predictive value using CT/MRI is reported to be as high as 87.3% and the positive predictive value as high as 82.6%.39 CT/MRI is helpful in detecting clinical ENE but is not proven reliable in predicting lesser degrees of ENE. Most prognostic information on ENE is based on pathologic ENE. Both microscopic ENE defined as ENE 2 mm or less beyond nodal capsule and major ENE defined as ENE more than 2 mm beyond nodal capsule qualify as ENE positivity for pathologic staging in the eighth edition.

COMPOSITE ANALYSIS OF RISK FACTORS IN ORAL CAVITY CANCERS

The oral cavity is the most common site of mucosal HNC, and treatment of oral cavity cancers is surgically driven. For OCSCC, Chen et al40 examined over 567 treated patients retrospectively and defined positive margin and ENE as major risk factors and pT4, positive nodes, close margin (≤ 5 mm and > 1 mm), tumor depth 1 cm or more, lymphatic invasion, vascular invasion, PNI, and poor differentiation as minor risk factors. By subgroups analysis, 192 patients with at least two minor prognostic factors and no other major risk factors benefitted from postoperative RT or concurrent chemoradiotherapy with significantly better 5-year LRC, DFS, and OS compared with the surgery-only group. For 179 patients with at least three minor prognostic factors and/or at least one major risk factor, patients receiving postoperative concurrent chemoradiotherapy showed significantly better 5-year LRC, DFS, and OS compared with postoperative RT or surgery alone. They concluded that patients with OCSCC with two minor risk factors should receive postoperative RT, and those with positive margin, ENE, or more than two minor risk factors have better outcomes with the addition of chemotherapy.40 In a multi-institutional study of patients with OCSCC with ENE, the addition of chemotherapy to radiation led to a 55% survival advantage at 5 years (p < .05).41

In another study of stage III and IV OCSCC, high-grade tumors (HR 1.81; p = .0285), recurrent tumors (HR 1.963; p = .0214), and tumors with higher nodal ratio (HR 1.037; p = .0240) were shown to be associated with inferior DFS. There is a broad list of risk factors reported important for DFS in OCSCC, which also include pattern of tumor invasion (WPOI),5 presence of lymphocytic host response (LHR), grade, and degree of keratinization.42 Tumors with strong LHR are densely rimmed with lymphocytes, with at least one lymphoid nodule at the tumor interface per low-power 4x microscopic field, and are correlated with stronger adaptive CD8+ T-cell immunity response against tumor antigens and more favorable tumor stage and survival. Added to this broad array of histopathologic features are more recent reports on genomic and molecular profiling of these cancers. This heterogeneity of factors has proven difficult for integrative risk modeling to better inform adjuvant treatment decisions. Recurrent OCSCC still remains a deadly disease, with 30% to 45% 5-year OS after salvage surgery.10

CONSIDERATIONS OF POSTOPERATIVE RT IN HPV-ASSOCIATED DISEASE

HNC epidemiology has undergone a major change over the last decade, with an increasing prevalence of HPVOPC in healthy, nonsmoking males. HPVOPC has a different demographic and biology than HPV-negative OPC, which is predominantly due to the carcinogenic effects of tobacco use. HPVOPC, usually diagnosed by positive p16 immunohistochemistry, is generally more sensitive to treatment, which gives patients with these cancers a survival advantage.44 The landmark Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) trials, which established margin positivity and extranodal extension as powerful negative prognostic factors for which adjuvant chemoradiotherapy is indicated, did not control for oropharynx subsite or HPV status. Whether positive margin or ENE, as classically defined, are important risk factors for HPVOPC is also of importance. Multiple smaller retrospective series have reported little benefit to the addition of chemotherapy to postoperative radiation.45-47 In one National Cancer Database study of 1,043 patients with OPC who underwent primary surgery, ENE, LVI, pT3 to T4 tumors, and Charlson/Deyo score were associated with inferior OS. However, OS was not better with adjuvant chemoradiotherapy compared with RT alone in the patients positive for ENE (89.6% vs. 89.3%, respectively; p = .55).48

Amini et al49 found that the presence of positive margin and/or ENE was associated with worse OS in HPV-negative OPC (HR 2.11; p = .008) but not HPVOPC (HR 1.61; p = .154). Ajmani et al50 examined the National Cancer Database records for 6,948 patients diagnosed with head and neck squamous cell carcinoma between 2010 and 2013 who underwent surgical resection and had either positive margins or ENE and found chemoradiotherapy beneficial over RT in ENE among patients with HPV-negative tumors and in positive margins among patients with HPV-positive tumors. For OPC and cancer of unknown primary, Kharytaniuk et al51 found ENE to be a considerably worse determinant of relapse-free survival (HR 9.7; 95% CI, 1.3–72.3) and DSS (HR 8.7; 95% CI, 1.1–62.7) in p16-negative cases. In contrast, among patients with p16-positive disease, ENE had no effect on relapse-free survival (HR 1.1; 95% CI, 0.2–7.8) or DSS (HR 1.2; 95% CI, 0.1–18.7).51 This question is being investigated in clinical trials. Rather than the presence of ENE being prognostic in resected HPVOPC, there is now evidence implicating a
number of involved metastatic nodes as more powerfully prognostic.\textsuperscript{52} This is reflected in the new American Joint Committee on Cancer eighth edition pathologic staging system for HPVOPC,\textsuperscript{52} in which patients with more than four nodes involved is the only factor that determines N2 disease as opposed to N1.\textsuperscript{52} In multivariable Cox analyses, ENE, N2c-N3 classification, and smoking were not prognostic. As there is potential added toxicity of trimodality therapy, there is pressing concern to exactly define what are high-risk prognosticators for HPVOPC justifying treatment intensification for this patient subpopulation. Su et al\textsuperscript{45} contend that the omission of concurrent chemotherapy to adjuvant RT may offer comparative local control rates with a lower toxicity profile in the setting of patients with HPV-positive disease with traditional high-risk features. However, one is cautioned that premature omission of chemotherapy may lead to increased distant relapse in HPVOPC.\textsuperscript{53}

Importantly, in a recent multi-institutional study of 53 patients with HPV-positivdisease treated with transoral robotic surgery who met indications for either adjuvant RT or chemoradiotherapy but refused, Routman et al\textsuperscript{54} found that patients without ENE or positive margins had an 11\% risk of failure using death as a competing event, whereas those with ENE had a 53\% risk of recurrence. Salvage therapy was successful in 77\% of patients. This underscores the fact that at least adjuvant RT is critical for patients positive for HPV with ENE and raises the question of whether all patients positive for HPV with intermediate-risk disease (PNI, LVI, T3 to T4, or N2 to -3 disease) require adjuvant RT at all. Perhaps patients with a single intermediate-risk factor (e.g., only PNI or two involved lymph nodes without ENE) can be safely treated with surgical monotherapy and reserve intensified strategies for salvage. This remains an open question that requires prospective study.

**ADJUVANT CHEMOTHERAPY: FOR WHOM SHOULD CHEMOTHERAPY BE ADDED TO ADJUVANT RT?**

Adjuvant RT improves outcomes; however, with RT alone, failure to cure remains common in higher-risk patients. Two landmark large randomized clinical trials addressed whether there was any benefit with the addition of chemotherapy: EORTC 22931\textsuperscript{55} and RTOG 9501.\textsuperscript{56} The regimen used in the two studies was identical (bolus cisplatin 100 mg/m\textsuperscript{2} every 3 weeks for three doses), but the inclusion criteria were different. Both studies allowed patients with positive margins or ENE. EORTC 22931 also allowed for inclusion of stage III or IV cancers, oropharynx or oral cancer with level 4 or level 5 lymphadenopathy, PNI, and vascular invasion. RTOG 9501 also allowed presence of at least two involved lymph nodes.

A recent retrospective analysis of 10,870 patients with stage III or IV squamous cell carcinoma of the head and neck treated surgically whose pathology report demonstrated positive margins or ENE, the addition of cisplatin to adjuvant RT offers a roughly 48\% reduction in the risk of locoregional relapse, 30\% improvement in DFS, and 30\% improvement in OS. Patients without positive margins or ENE but with multiple positive lymph nodes do not appear to benefit. It is unclear whether patients with stage III to IV cancer, level 4 or 5 lymphadenopathy, perineural disease, or vascular invasion benefit from chemotherapy. At tumor boards and in examination rooms, chemoradiotherapy is often considered for patients without positive margins or ENE. A recent retrospec\textsuperscript{57} tive observational cohort study using the National Cancer Database evaluated over 10,870 patients with stage III or IV squamous cell carcinoma of the head and neck treated surgically whose pathology report did not show positive margins or ENE.\textsuperscript{58} A total of 47\% were treated with chemoradiotherapy, and survival was superior for those treated with chemoradiotherapy (HR 0.9; p < .001). Increasing number of involved lymph nodes was associated with increased benefit.

**HARD CHOICES: PATIENTS WITH CISPLATIN CONTRAINDICATIONS**

Any treatment advantages come at high toxicity cost, rendering some patients ineligible or borderline eligible. Cisplatin is a very toxic chemotherapeutic agent. In the RTOG 9501 study, the rate of grade 3 to 5 acute toxicities with RT alone was 34.4\%. This rate rose to 77\% with the addition of cisplatin to RT, including two deaths.\textsuperscript{59} Acute grade 3 to 5 toxicities increased by at least 10\% including: hematologic (1\% vs. 78\%), mucous membrane (37\% vs. 62\%), pharynx and esophagus (32\% vs. 50\%), nausea and vomiting (0\% vs. 40\%), upper gastrointestinal tract (6\% vs. 32\%), infection (1\% vs. 13\%), and neurologic (0\% vs. 10\%). In clinical practice, long-term otopathy, nephropathy, and neuropathy are also commonly seen.\textsuperscript{60} The RTOG subsequently updated the incidence of chronic toxicities grade 3 to 5 at 1, 2, 5, and 10 years.\textsuperscript{57} They were 12\% versus 20\% at 1 year, 16\% versus 0.8; p = .19). In subsequent 10-year reanalysis, no treatment advantage remained for any of these measures (LRC: HR 0.7, p = .1; DFS: HR 0.9, p = .25; and OS: HR 0.9, p = .3).\textsuperscript{57} In unplanned analysis of the subgroup with either microscopic positive margins or ENE, LRC and DFS improved, and OS trended toward improvement (LRC: HR 0.5, p = .02; DFS: HR 0.8, p = .05; and OS: HR 0.8, p = .08). In patients who met entry criteria by having two or more positive nodes but without positive margins or ENE, there were no trends or even hints of improved outcomes with the addition of cisplatin to adjuvant RT. Subsequently, a joint analysis of these two major trials was conducted.\textsuperscript{58} It showed that patients with positive margins or ENE clearly benefitted from the addition of chemotherapy to adjuvant radiation (combined HR for LRC, 0.5; for OS, 0.7; both significant with p values not provided). Among patients eligible for the RTOG study only, there was no hint of improvement in treatment outcomes, whereas there was a trend toward improved LRC (HR 0.5; p = .1) and OS (HR 0.7; p = .06).

In summary, for the fit patient with a surgical pathology report demonstrating positive margins or ENE, the addition of cisplatin to adjuvant RT offers a roughly 48\% reduction in the risk of locoregional relapse, 30\% improvement in DFS, and 30\% improvement in OS. Patients without positive margins or ENE but with multiple positive lymph nodes do not appear to benefit. It is unclear whether patients with stage III to IV cancer, level 4 or 5 lymphadenopathy, perineural disease, or vascular invasion benefit from chemotherapy.
21% at 2 years, 19% versus 23% at 5 years, and 21% versus 25% at 10 years.

Finally, many patients with head and neck squamous cell carcinoma are considered poor candidates for high-dose cisplatin due to advanced age, baseline renal dysfunction, known auditory deficits including hearing loss and/or tinnitus, and poor performance status. The optimal treatment of the patient for whom adjuvant chemoradiotherapy is indicated but bolus cisplatin contraindicated is poorly defined.

No phase III study addresses this population, and so the clinician is left with regimens evaluated in phase II studies, with modified regimens, or with extrapolation from data sets derived from the definitive context. In the definitive context, the addition of cetuximab to RT improved survival, but no large randomized data exist in the adjuvant context. The best available data to address the question of cetuximab’s merits in adjuvant chemoradiotherapy come from the randomized phase II RTOG 0234. RTOG randomly assigned 238 patients with positive margins, extracapsular extension, and/or multiple involved lymph nodes to weekly cetuximab plus cisplatin 30 mg/m² or to weekly cetuximab plus docetaxel 15 mg/m². For the cisplatin plus cetuximab arm, 2-year DFS was 57%, and 2-year OS was 69%. For the docetaxel plus cetuximab arm, 2-year DFS was 66%, and 2-year OS was 79%.

FUTURE DIRECTIONS FOR INTERMEDIATE-RISK POSTOPERATIVE PATIENTS

Several clinical trials are open and investigating novel approaches to patients with intermediate-risk disease. RTOG 0920 (NCT00956007) is randomly assigning patients with medium risk to radiation alone or to radiation plus cetuximab. Medium risk in this study is defined as absence of positive margins or extracapsular extension but presence of one of the following: PNI, LVI, single lymph node more than 3 cm or two or more lymph nodes (all < 6 cm), close margin(s) of resection, pathologically confirmed T3 or T4a primary tumor, or T2 oral cavity cancer with more than 5 mm DOI.

The Eastern Cooperative Oncology Group-ACRIN Cancer Research Group EA3132 (NCT02734537) trial is a randomized trial of intermediate-risk patients (without ENE or positive margins) who have disruptive p53 mutations, which confer a poorer prognosis, to be treated with either RT alone or RT plus cisplatin with the hopes of improving DFS in this cohort.

The RTOG 1216 (NCT01810913) trial is investigating cisplatin compared with docetaxel compared with docetaxel plus cetuximab in high-risk patients who have undergone resection of HPV-negative HNC and have positive margins or ENE. This phase III trial is ongoing.

The NRG-HN003 (NCT02775812) is investigating the addition of pembrolizumab to radiation and cisplatin in high-risk patients as well. This initial phase I study is nearly completed accrual and may be incorporated into the 1216 trial as an additional arm.

LCCC1725 is a phase II study of adjuvant RT with the PD-L1 inhibitor durvalumab and the CTLA-4 inhibitor tremelimumab for medium-risk patients. In this study, medium risk is defined similarly to RTOG 0920, with the exception that T2 oral cavity with more than 5 mm DOI is not included. The study is expected to start accrual in the spring of 2018.

PATHWay (NCT02841748) is a randomized, double-blinded phase II study of 1 year of pembrolizumab or placebo. Inclusion criteria are very broad, encompassing a variety of populations with risk of recurrence of at least 40%, including postoperative patients. Of note, pembrolizumab treatment follows complete standard therapy and is not given concurrently with RT.

CONCLUSION

Our understanding of HNCs is evolving. Adjuvant RT and chemoradiotherapy have a defined role in this disease with known indications. However, these are in flux based on HPV status, genomic biomarkers, and novel agents. Future trials are investigating many of these questions. The dual objectives of optimizing cancer and quality-of-life outcomes require multidisciplinary engagement in both clinical practice and investigational arenas.

References


HEALTH SERVICES RESEARCH, CLINICAL INFORMATICS, AND QUALITY OF CARE
Communicating the Financial Burden of Treatment With Patients
Ryan D. Nipp, MD, Ellen Miller Sonet, MBA, JD, and Gery P. Guy Jr., PhD, MPH

OVERVIEW
In recent years, high health care costs and the financial burden of cancer care have received increased attention. In response to the financial burden of cancer care, patients may jeopardize their health outcomes by not properly adhering to prescribed therapies or even forgoing and delaying care in an effort to defray costs. In addition, the financial burden experienced by patients with cancer may negatively impact clinical outcomes, such as quality of life, physical and psychological symptoms, and potentially, even survival. Notably, in the current era of targeted treatment and immunotherapies for patients with cancer, the rising costs of cancer continue to remain at the forefront of patient concerns. Therefore, a critical need exists to determine how best to assist patients with the cost burden of cancer diagnosis and treatment.

As data mount showing that patients with cancer often experience financial burden related to their care,1-4 there is a growing need to foster appropriate patient-clinician communication about the costs of cancer care.5-18 Research has shown that oncologists frequently feel uncomfortable and poorly equipped to discuss costs with their patients.17,18 As a result, oncology clinicians often do not ask about their patients’ financial concerns.18-20 However, the majority of oncologists acknowledge the importance of discussing the financial impact of care with patients.18 Importantly, published recommendations from ASCO and others encourage patient-clinician discussion about the costs of cancer care.21,22 Notably, patient-clinician discussion about the costs of cancer care has the potential to improve care delivery and outcomes for patients by fostering informed decision-making. Although the financial costs of cancer care represent just one factor in the decision-making process, data suggest that patients would appreciate the opportunity to engage in financial discussions with their oncology team.19,23,24 In addition, patients often prefer that their clinician initiate cost discussions with them rather than initiating the conversations themselves.25

THE CLINICIANS PERSPECTIVE ON DISCUSSING COSTS WITH PATIENTS
Potential Barriers to Cost Discussions
Multiple hypothetical barriers exist that often prevent oncologists from engaging in discussions about the costs of cancer care with their patients (Sidebar 1). First, clinicians may worry that these discussions are time consuming. In a time-limited clinical encounter, oncologists may prioritize discussions about other issues, such as their patients’ physical symptoms, the side effects of treatment, laboratory and imaging results, and chemotherapy dosing. Second, clinicians may avoid discussions about the costs of cancer care because of their lack of knowledge about the total costs incurred by the patient and the specific out-of-pocket expenditures that patients may endure. Certain patients may have different insurance plans and benefit packages that alter the amount that a specific individual will ultimately pay for their cancer care, and this further complicates clinicians’ ability to anticipate the economic consequences for each individual patient. Third, some clinicians may feel that they should not consider costs when making treatment recommendations for their patients from both a practical and an ethical point of view.26,27 Similarly, oncologists may defer cost discussions with their patients out of concern that some patients may forgo potentially beneficial cancer care because of cost concerns. In addition, oncology clinicians do not want their patients to think that they are willing to compromise the quality of their care because of costs. However, for patients to make truly informed decisions about their care, information about costs is a side effect that patients may need and want. Importantly, research has shown that patients do not often let their out-of-pocket expenses influence their decision-making regarding their cancer care.23

Patients also experience hypothetical barriers that prevent them from engaging in cost discussions. Specifically, patients may not feel comfortable raising the issue of their

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The costs of cancer care have risen over time and may continue to worsen in the current era of targeted therapies and immunotherapies. As the cost of cancer treatment continues to increase, ongoing efforts are needed to enhance our understanding of the financial hardship experienced by patients with cancer and their families to identify potential solutions.

Conversations between clinicians and patients about the financial consequences of cancer treatment are fundamental to high-quality, patient-centered cancer care, and may help address patients' financial burden.

Potential barriers may exist that prevent patient-clinician discussions about the cost of cancer care.

Despite the potential barriers to patient-clinician cost discussions, practical solutions exist that may improve patients' and clinicians' abilities to communicate about the cost of cancer care.

Financial concerns because of uncertainty about the appropriateness of discussing this issue with their clinical team. Similarly, patients may feel embarrassed and self-conscious about the notion that costs represent one of their concerns, especially in the setting of cancer when other issues may seem more pressing at times. Moreover, patients want to respect their clinicians’ time, and if they feel that their oncologists are too busy or lack solutions for this problem, this may further prevent patients from attempting to engage in discussions about the cost of their cancer care. If patients sense that they have limited time to discuss all of their issues with their clinicians, they may prioritize issues that they feel more confident that their team can address, such as physical symptoms, medication management, and questions about their treatment. Notably, patients may not know the full extent of the financial implications of their care until much later, and thus, they may not know to mention their cost concerns until it is too late for them or their clinical team to help defray some of the expenses.

**Potential Solutions to Assist With Patient-Clinician Discussions About Costs**

Despite the various barriers to patient-clinician cost discussions that exist, a few practical solutions have emerged to enhance patients’ and clinicians’ abilities to communicate about the costs of cancer care. Currently, oncology clinicians receive little training about the financial burden of cancer. Thus, a first step in fostering patient-clinician discussions about costs could include providing additional training for clinicians about the economics of cancer care and basics of health insurance, in addition to assisting clinicians with how to engage in cost discussions with their patients. Research suggests that clinicians who report feeling more comfortable discussing costs with their patients are then more likely to engage in cost discussions with their patients. Notably, in cancer care, clinicians often have limited options when selecting the best treatment strategy for their patients. However, in those instances when multiple, equally effective treatment options exist, clinicians should be equipped with the relative costs of the different options to aid in decision-making discussions. In addition, simply providing patients with the time costs, such as time away from home and frequency of clinic visits for certain regimens, may add valuable information for patients to consider when making informed treatment decisions about their care. Furthermore, clinicians often experience time constraints that limit their ability to engage in discussions about patients’ cost concerns. Thus, efforts to effectively address patients’ financial burden could include the use of nonclinician support staff, such as financial counselors or other trained administrative staff, to meet regularly with patients and help strategize about options to limit the financial burden associated with cancer care. Financial counselors have the ability to inform patients about cancer treatment costs, their insurance benefits, and anticipated out-of-pocket expenditures for treatment. Additional research is needed to understand the impact of efforts, such as integrating financial counselors into clinical care.
the cancer care team and/or training clinicians to engage in costs discussions, on the financial distress experienced by patients with cancer.

**COST IN THE ERA OF TARGETED THERAPIES AND IMMUNOTHERAPIES FOR CANCER**

Cancer care costs have risen substantially over time. Notably, the cost of cancer care has increased at two to three times the rate of other health care costs. From 1965 to 2013, the average monthly cost of cancer treatment increased from $100 to $10,000. Importantly, as the availability and use of expensive targeted therapies and immunotherapies steadily rise, we are likely going to continue to see an upward trend in cancer treatment costs. Although these therapies bring new hope in the fight against cancer, higher treatment costs could also result in considerable out-of-pocket expenses and financial hardship among patients with cancer and their families.

Cancer survivors (individuals with a history of cancer) have greater medical expenditures and out-of-pocket costs than individuals without a history of cancer, regardless of insurance status. In addition, research has shown that survivors continue to experience financial burden for many years after their initial cancer diagnosis and treatment, reflecting their need for care to address the late and lasting effects of cancer treatment. Most health insurance plans require some form of cost-sharing for cancer therapy (typically in the form of a copayment), thus patients and their families may be responsible for thousands of dollars in medical bills for their cancer treatment. In recent years, out-of-pocket costs for cancer treatment have risen dramatically, even among patients with health insurance coverage.

**TABLE 1. Characteristics of Selected Publicly Available Data Sources for Estimating the Financial Burden Associated With Cancer Care**

<table>
<thead>
<tr>
<th>Data Characteristics</th>
<th>Surveillance Epidemiology and End Results Medicare</th>
<th>National Health Interview Survey</th>
<th>MEPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Data Collection</td>
<td>Cancer registries linked to Medicare claims</td>
<td>Self-reported</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Self-reported, provider reported</td>
<td></td>
</tr>
<tr>
<td>Availability</td>
<td>Annually</td>
<td>Annually</td>
<td></td>
</tr>
<tr>
<td>Representativeness</td>
<td>Geographically defined</td>
<td>Nationally representative</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Age 65 and older and disabled (all ages)</td>
<td>Age 18 and older</td>
<td></td>
</tr>
<tr>
<td>Health Insurance Type</td>
<td>Only Medicare fee for service</td>
<td>All payers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>All payers</td>
<td></td>
</tr>
<tr>
<td>Financial Burden Information Included</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical expenditures</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inpatient costs</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Outpatient costs</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pharmacy costs</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Out-of-pocket costs</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Productivity loss</td>
<td>Employment disability*</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>Days lost from work</td>
<td>x</td>
<td></td>
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<tr>
<td></td>
<td>Lost household productivity</td>
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<td></td>
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<tr>
<td>Medical care use</td>
<td>Delaying medical care because of cost</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Not receiving medical care because of cost</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Changing prescription use because of cost</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Financial hardship because of cancer</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Medical debt</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Bankruptcy</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Trouble paying medical bills</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Making financial sacrifices</td>
<td></td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Worry about paying medical bills</td>
<td></td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

*Available in the MEPS Experiences With Cancer Survivorship Supplement.

*Being unable to work because of health.
The high cost of cancer treatment may pose an even greater challenge among those without health insurance, because they are likely to face even higher out-of-pocket costs.39 High out-of-pocket costs can reduce access to care, influence clinical practice, and affect treatment choices.17,40 By creating a financial barrier, high out-of-pocket costs can also result in patients delaying medical treatment and missing the opportunity to obtain necessary care.10,41,42 Data suggest that nearly one-third of cancer survivors report making changes in their prescription drug use (i.e., skipping doses, taking less medicine, delaying filling a prescription, asking for lower-cost medication, buying prescription drugs from another country, and using alternative therapies) for financial reasons.43 Furthermore, reduced access to care among cancer survivors may affect surveillance for disease recurrence, screening for additional cancers, and care for the late and lasting effects of cancer treatment.44,45

In addition to high out-of-pocket costs, a cancer diagnosis may also limit employment opportunities.46 Cancer survivors are more likely to report being unable to work, missing more days of work, and spending more days in bed because of their health compared with those without a history of cancer.52 Given the strong relationship between employment and health insurance, the inability to work could result in the loss of insurance and fewer resources to pay for medical care, further magnifying the financial hardship associated with cancer. Notably, patients with cancer are at increased risk for financial hardship, such as reduced income (because of loss of work), medical debt, and even bankruptcy.3,47-49 Among working age cancer survivors, research has shown that over one-fourth report material financial hardship (i.e., medical debt, bankruptcy, trouble paying medical bills, and making other financial sacrifices) because of their cancer diagnosis and its treatment.49 Moreover, data have shown that approximately one-third of cancer survivors report going into debt as a result of their cancer, and 3% have filed for bankruptcy as a result of cancer.64 In addition, 23% of cancer survivors and 32% of working age cancer survivors report worrying about paying large medical bills.48 Such concerns surrounding cancer treatment costs are common among patients with cancer, even those with health insurance.50 The financial strain associated with cancer treatment can have a substantial impact on the quality of life of patients and their families.31,52 Importantly, as a result of the remarkable financial burden of cancer, patients and their families may be faced with choosing between cancer therapies or paying their daily living expenses.2,53

Assessing Financial Burden Among Patients With Cancer
In the current era of targeted therapies and immunotherapies for patients with cancer, the financial burden of cancer care is likely to continue to worsen. However, research focused on the financial burden related specifically to targeted therapies and immunotherapies is lacking. With the increasing cost of cancer treatment, it is critical for ongoing efforts to continue to monitor and improve our understanding of the financial hardship faced by patients with cancer and their families. Importantly, a number of publicly available data sources are available to examine the financial burden associated with cancer care (Table 1), such as the Surveillance Epidemiology and End Results Medicare data, the National Health Interview Survey, and the Medical Expenditure Panel Survey (MEPS).

**Surveillance Epidemiology and End Results Medicare**
Surveillance Epidemiology and End Results Medicare data, available from the National Cancer Institute, provide detailed information about Medicare beneficiaries with cancer. This combined data set contains information about medical care and the costs of treatment before a cancer diagnosis, over the course of treatment, and during long-term follow-up.54 These data have been used extensively to estimate the costs of cancer treatment among Medicare beneficiaries.33,55 Thus, the Surveillance Epidemiology and End Results Medicare combined data set represents a helpful tool for clinicians and researchers to continue to investigate the financial burden of cancer care in the current era of targeted therapies and immunotherapies.

**The National Health Interview Survey**
The National Health Interview Survey is an annual nationally representative survey of the adult population in the United States conducted by the Centers for Disease Control and Prevention. The National Health Interview Survey contains information on a broad range of health topics and includes

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**SIDEBAR 2. Assisting Patients With the Cost Burden of Cancer Diagnosis and Treatment**

**Strategies to Alleviate Financial Burden**
1. Provide information on helpful resources
2. Include information and resources in clinics, waiting areas, and online portals
3. Screen for risk of financial toxicity (e.g., distress thermometer or the COST tool)
4. Refer to a financial navigator and/or oncology social worker

**Strategies to Communicate With Patients About Costs**
1. Ask patients if they are concerned about the costs of treatment and related expenses
2. Explain that nearly all patients find it difficult to manage these costs; show empathy
3. Discuss lower-cost treatment options and alternate dosing and testing schedules, if available
4. Discuss patients’ lifestyle priorities and preferences
5. Regularly mention available resources to help with financial challenges
detailed demographic and socioeconomic characteristics. In addition, the National Health Interview Survey provides information about patient-reported financial concerns related to health care access and affordability. The data have been used previously to assess a wide range of issues affecting cancer survivors, including employment, activity limitations, insurance coverage, and access to care.\textsuperscript{34,41,43,56-58}

**The Medical Expenditure Panel Survey**

The MEPS household component is an annual, nationally representative household survey conducted by the Agency for Healthcare Research and Quality.\textsuperscript{59} In addition to information on demographic characteristics, health status, access to medical care, and employment, the MEPS collects information on health care use and expenditures among adults of all ages, regardless of insurance status. The MEPS data have been used to examine several aspects of the burden of cancer, including the economic burden among cancer survivors, out-of-pocket costs, patient time costs, and access to preventive care.\textsuperscript{34,42,60,61}

In an effort to improve the quality of data available for estimating the burden of cancer in the United States, the MEPS Experiences with Cancer Survivorship Supplement was recently developed.\textsuperscript{62} The MEPS Experiences with Cancer Survivorship Supplement is a self-administered questionnaire of adult cancer survivors containing questions on medical care costs, employment patterns, financial hardship, and the burden of illness for cancer survivors and their families.\textsuperscript{62} These data, first collected in 2011, have been used to examine issues facing cancer survivors, such as access to care,\textsuperscript{63} and the financial hardships related to cancer treatment.\textsuperscript{49}

**Future Work**

As the cost of cancer treatment increases in the United States, the financial burden associated with treatment will likely increase in tandem. Thus, estimating and projecting the financial burden of cancer will be increasingly important and timely issues. Emerging areas for future research include evaluating the use, effectiveness, and consequences of targeted therapies and immunotherapies. Estimating treatment uptake, associated costs, and the impact of financial burden on patient morbidity and survival are important areas for future research.

### ASSISTING PATIENTS WITH THE COST BURDEN OF CANCER DIAGNOSIS AND TREATMENT: NEXT-GENERATION SEQUENCING TESTING, OFF-LABEL MEDICATIONS, AND MORE

Conversations between clinicians and patients about the financial costs of treatment are fundamental to high-quality, patient-centered cancer care. The National Academies of Medicine highlighted the issue of the financial costs to patients in the 2013 Consensus Study Report entitled Delivering High-Quality Cancer Care: Charting a New Course for a System in Crisis.\textsuperscript{21} Subsequently, substantial research has focused on defining, assessing, and characterizing the impact of what is artfully termed “financial toxicity.”\textsuperscript{64} The Comprehensive Score for Financial Toxicity (COST) measure is a well-validated, 11-item questionnaire that helps identify patients with cancer who may be at greater risk for experiencing financial toxicity.\textsuperscript{64} Notably, financial toxicity has been linked to reductions in health-related quality of life,\textsuperscript{62} symptom burden,\textsuperscript{11} treatment compliance,\textsuperscript{5} and even survival.\textsuperscript{13} However, despite the compelling data attesting to the perils associated with the financial burden of cancer, efforts to respond to this particularly troubling side effect of cancer treatment are lacking.\textsuperscript{65}

Even before a cancer diagnosis is confirmed, health care expenditures and financial burdens represent a major concern for many patients. For individuals who are still seeking to confirm their diagnosis, surveys have shown that nearly one-half talked with their physician or office staff about the cost of testing before they had the test, and over one-fifth did not follow their doctor’s test recommendations because of the costs of care.\textsuperscript{66} Furthermore, finances can cause considerable psychological distress for patients.\textsuperscript{64} Research suggests that nearly one-third of patients with advanced cancer report financial distress to be more severe than their physical, family, and emotional distress.\textsuperscript{67} Notably, the presence of financial distress has been shown to correlate with patients’ anxiety, depression, and quality of life.\textsuperscript{51,52,67} Patients often face numerous stressors related to the diagnosis of cancer, such as the ability to cope emotionally and trying to find a “new normal” while adjusting to the reality of their illness. When experiencing financial distress, patients’ capacity to integrate and accept their diagnosis may be compromised as they direct their attention toward paying for treatment and related expenses.\textsuperscript{68} Thus, developing and testing ways to help patients and clinicians communicate about the financial burden of cancer treatment are increasingly important.

Despite the prevalence of financial distress and the impact that it has on patients’ quality of life and outcomes, treatment costs and patients’ financial distress are rarely probed by oncology clinicians.\textsuperscript{69} In addition, patients may avoid engaging in cost discussions with their clinicians.\textsuperscript{17} Although many resources exist to support patients and address their financial concerns, clinicians often lack knowledge about these resources and/or forget to bring them to the attention of their patients. In fact, survey data suggest that fewer than one-half of patients report having enough information about the costs of their treatment plan.\textsuperscript{66} Importantly, oncology clinicians often avoid discussing costs with their patients, because they worry about not having viable ways of addressing their patients’ cost concerns. However, options do exist for clinicians to potentially help address their patients’ financial burden, such as switching patients to lower-cost medications when possible, choosing alternative treatment schedules, facilitating copay assistance, and arranging tests, visits, and procedures to avoid paying multiple deductibles (Sidebar 2).\textsuperscript{65} In addition, other care team members can help provide advice to patients,
including patient financial services staff and primary care clinicians. Patients generally find that any advice to help with affording medical bills is helpful.

In summary, additional work is needed to determine the best strategy for oncologists to engage in cost discussions with their patients. Aside from direct conversation between care team members and patients regarding finances, other opportunities exist to address the financial hardships that patients face. Clinicians can use certain strategies and/or recommend resources to help patients cope with financial hardship and its accompanying distress, including the following.

1. Clinicians can consider distributing a list of financial and psychosocial support services to patients either before or during their initial visits. Information about these resources should also be available in clinics, waiting areas, and online portals as part of comprehensive patient education.

2. Clinicians and researchers can use tools, such as the COST measure and/or distress thermometer, to determine patients’ risk for “financial toxicity” and other indicators of stress. These assessments can help clinicians identify patients at greatest need for certain support services.

3. Clinicians can consider referring patients for financial counseling, and many hospitals and practices are beginning to offer financial navigation services.

4. Referring patients and caregivers to oncology social workers can help them manage the enormous strain of a cancer diagnosis and its impact on all aspects of their life.

5. When internal resources are not available, clinicians could consider referring to external organizations to help with their patients’ financial burden and distress.

6. Clinicians should be informed about the costs of treatment, as this may help them learn about the presence of lower-cost treatment options. In addition, clinicians should be open to discussing patients’ financial concerns, which will help patients understand that they are sensitive to the financial challenges of cancer and empower patients to discuss their concerns with care team members.

References


Patient-Clinician Communication Is a Joint Creation: Working Together Toward Well-Being

Timothy Gilligan, MD, Liz Salmi, and Andrea Enzinger, MD

OVERVIEW

Oncology clinicians face a monumentally difficult task: to guide patients on what may be the scariest and most unpleasant journey of their lives. They must preserve their patients’ hope while at the same time giving them accurate information. And patients with cancer face a monumentally difficult task: navigating a path while confronting an often-terrifying disease. Communication between patients with cancer, their loved ones, and the treating clinicians presents many challenges. We must become better at communicating with each other; patients need easier access to information about their medical condition and their health care; and we must establish relationships that are stronger and more respectful, trusting, and empathic. If we are to deliver patient-centered or whole-person care, we must know who our patients are, what is important to them, and how they derive meaning in their lives. In this review, we discuss ASCO’s first Patient-Clinician Communication guideline, the importance and value of patients having direct access to their medical record, and how to address spirituality and/or religion with patients with cancer.

Oncology clinicians face a monumentally difficult task: to guide patients on what may be the scariest and most unpleasant journey of their lives. They must preserve their patients’ hope while at the same time giving them accurate information. And patients with cancer face a monumentally difficult task: navigating a path while confronting an often-terrifying disease, and having to work with a health care system that often seems bureaucratic and uncaring.

Communication between patients with cancer, their loved ones, and the treating clinicians presents many challenges. The medical and emotional stakes are high, and there is generally a large disparity in expertise—the patients know more about themselves, their life, and their values, and the clinicians know more about medicine. In addition, most patients have not faced a cancer diagnosis before, and many clinicians have received little if any high-quality training in how to talk to patients and colleagues in a manner that fosters strong, trusting relationships.

A further challenge is the strong move away from a paternalistic model of medicine. Under this model, the physician was assumed to know best and patients were often assumed to be too fragile or too lacking in medical expertise to be able to handle hearing the truth about their condition. Fast forward to the present, and we find ourselves in a world where patients are increasingly recognized as members of the care team who have an essential role to play as experts in their own experience, history, and values.

To adapt to this new world, several things are needed. We must become better at communicating with each other; patients need easier access to information about their medical condition and their health care; and we must establish relationships that are stronger and more respectful, trusting and empathic. If we are to deliver patient-centered or whole-person care, we must know who our patients are, what is important to them, and how they derive meaning in their lives. With regard to the first challenge above, ASCO issued its first Patient-Clinician Communication guideline in 2017; it is discussed below. Second, Liz Salmi, a patient with cancer, writes about the importance and value to patients of having direct access to their medical record, including clinician notes. Finally, the article discusses how to address spirituality and/or religion with patients with cancer.

ASCO PATIENT-CLINICIAN COMMUNICATION GUIDELINE

The ASCO patient-clinician communication guideline was developed by a multidisciplinary, multiprofessional panel that included representation from medical oncology, psychiatry, nursing, hospice, and palliative medicine, as well as a patient representative and experts in health care communication and health disparities. The guideline was based on a systematic review of the literature and was developed using a formal consensus process. It is structured around nine key areas and makes specific recommendations within each of
these categories. The nine key areas are core communication skills, discussing goals of care and prognosis, discussing treatment options and clinical trials, discussing end-of-life care, using communication to facilitate family involvement in care, meeting the needs of underserved populations, communicating effectively when there are barriers to communication, discussing cost of care, and clinician training in communication skills.

A common theme linking most of these topics is relationship-centered communication (RCC) skills. RCC aims to facilitate patient-clinician interactions by developing a strong therapeutic relationship based on trust, caring, and mutual respect. Key RCC skills include rapport-building, listening, conveying empathy, and partnering with the patient with regard to setting the agenda for the visit and developing the treatment or management plan. The specific recommendations for each of the key areas are described below.

Core Communication Skills
These skills apply to almost every conversation. They include prework: reviewing the patient’s medical information, clarifying one’s own goals for the conversation, and anticipating the needs and responses of the patient and family. Core skills also include behaviors that actively foster trust and collaboration, such as sitting down, listening, and getting to know the patient as a person beyond their illness. The guideline recommends taking time at the beginning of encounters to inquire what the patient wants to address during the visit so that an agenda can be set collaboratively. Exploring patients’ understanding of their condition is also recommended so that the discussion can start from a place of shared understanding and misunderstandings can be addressed. When providing information, it should be timely and oriented to the patient’s concerns and preferences for information. Patients often complain that they have difficulty obtaining clinical information when they want it and are sometimes subjected to data-dumps whereby they receive more information than they can understand and retain. Retention can be improved by using “teach-back,” which is the practice of asking patients to tell the clinician how they would explain their condition and/or treatment plan to someone else. The final core skill is to respond empathically when patients display emotion.

Discussing Goals of Care and Prognosis
Oncology clinicians have a responsibility to develop treatment plans that align with the patient’s values and priorities. Patients cannot participate meaningfully in clinical decision making unless their goals are clearly defined and they understand the likely outcome of each of the options available to them. We must find out who our patients are as individuals, what is most important to them, and what they want from their health care team. Complicating matters, surveys of patients have made it clear that patients generally want accurate and candid information about their prognosis and also want information communicated in a way that sustains hope. Sustaining hope while providing candid information about a cancer’s prognosis can be challenging. It is appropriate to have a goals-of-care conversation whenever there is a substantial change in the condition or when considering a substantial change in treatment. The guideline has several recommendations for these conversations:

1. The core skill of asking patients about their current understanding of their condition and their prognosis can help clinicians frame medical information in a way that is more individualized to the specific patient. When the news is bad, this skill can alert the clinician as to how much of a surprise the news will be.
2. Asking what patients want to know and how much information they desire helps the clinician tailor the information delivered to fit the specific patient’s needs.
3. Clinicians can support hope by articulating their commitment to help and care for the patient throughout the course of the illness and to strive to obtain as good an outcome as possible.
4. When discussing prognosis, mixed framing and providing the information in small, discrete doses can improve patient understanding and recall. One example of mixed framing is to tell the patient the best, worst, and most likely outcome.
5. Clinicians should be prepared to respond empathically to patients’ emotional responses during or after these weighty conversations. When providing bad news, there are specific steps specified in the guideline that can improve the patient’s understanding and experience.

Discussing Treatment Options and Clinical Trials
Understanding their treatment options can be challenging for patients and studies have reported that patients accurately
remember well under half of the information they are given at health care visits. Several steps can help increase patient understanding and retention of information:

1. Clarifying the goal(s) of care and the expected outcome of each option (e.g., cure vs. prolongation of survival vs. improved quality of life).
2. Presenting benefits (e.g., longer life, delay of progression, symptom improvement) and burdens of treatment (e.g., side effects, cost, invasive procedures, time spent away from home in medical institutions and traveling to and from appointments) so that patients can balance them in light of their goals and priorities.
3. Delivering information about treatment options in small chunks and checking frequently for understanding.
4. Presenting standard treatment options, including palliative care, prior to investigational options so that patient understands what the clinical trial is an alternative to.

**Discussing End-of-Life Care**

Discussions of end-of-life care can be emotionally fraught for patients and loved ones and clinicians alike. The guideline makes several recommendations to facilitate these critical conversations. Using an organized framework can provide a structure that promotes higher-quality conversations and greater participation from patients and their loved ones. Just as when placing a central venous catheter or removing a gallbladder, clinicians will generally feel more confident if they have a clear understanding of what the key steps are and the order in which they should be undertaken. The guideline recommends initiating conversations about end-of-life preferences early in the course of a terminal disease and exploring how each patient’s culture and religion or spirituality affect their preferences regarding care near the end of life. Anticipating grief and distress among patients and their loved ones is appropriate, and an empathic response is important. Clinicians can be more effective in helping terminally ill patients if they are familiar with and inform patients about local resources available to provide support for terminally ill patients and their loved ones.

**Using Communication to Facilitate Family Involvement in Care**

Cancer affects not only the patient but the patient’s families and loved ones. Key decisions about treating and caring for the patient often have strong input from all of these parties. And families and loved ones often play a critical role in cancer care by providing care and support to the patient in many different ways. They also help by being another set of ears to hear medical information and thus help the patient remember and adhere to the treatment plan. And they are often a key source of important information about how the patient is doing at home. The guideline recommends encouraging involvement by family and loved one in discussions about goals of care and treatment early in the course of the disease if the patient consents. Formal family meetings are also recommended to help build a shared understanding of the patient’s condition, prognosis and goals of care, and end-of-life care preferences.

**Meeting the Needs of Underserved Populations**

There is abundant documentation of substantial racial and socioeconomic disparities in cancer care and cancer outcomes. The guideline includes three recommendations to improve communication with underserved populations. First, clinicians should maintain awareness that patients may have beliefs, experiences, understandings, and expectations that are different from the clinicians’. Curiosity about the patient and a sincere desire to understand them help build trusting relationships. Second, avoiding assumptions about sexual orientation and gender identity can help make all patients feel welcome and cared for. Similarly, clinicians should use nonjudgmental language when discussing sexuality and sexual behavior. Third, clinicians can build a more empathic relationship with members of underserved or marginalized populations by remembering that such patients are more likely to have had negative experiences with health care in the past, including experiences of feeling disrespected or unsafe. When patients have had such experiences in the past, it can take longer to build a trusting relationship.

**Communicating Effectively When There Are Barriers to Communication; Discussing Cost of Care**

When patients don’t share a common language with the clinician or have low health literacy or numeracy, communication about health care is more challenging. Attending to these issues by being rigorous in using trained medical interpreters, visual aids, and terminology the patient understands can all help. For a substantial proportion of patients, medical costs are a substantial burden. However, there are very limited data to guide best practices regarding talking to patients about cost of care, and some patients do not wish to discuss such matters with their oncologist. The guideline recommends exploring with patients whether cost of care is a concern and whether they want help learning more about the costs of their treatment and exploring options for covering those costs.

**Clinician Training in Communication Skills**

Health care communication is highly complex, and high-quality training can help clinicians improve. Such training should be based on sound educational principles and should include abundant opportunities to practice skills in simulated-patient scenarios, observed patient encounters, and other experiential learning opportunities. In teaching communication skills, the goal is not so much for the clinician to understand key principles of communication but rather to be able to use effective communication skills in practice. Learning to communicate is thus similar to learning to play a musical instrument or a sport. Lectures have not been demonstrated to be of any benefit; skills practice enables clinicians to improve.

When communicating with patients, clinicians bring their own history of experiences and their own biases and
sensitivities. Communication skills training is most effective if it fosters self-awareness and situational awareness related to emotions, attitudes, and underlying beliefs that may affect communication and decision-making. Teaching communication skills is complex and demanding work, and faculty of such educational sessions should be appropriately trained and experienced to be able to model and teach the desired skills and facilitate experiential learning.

ANCHORING PATIENT CONVERSATIONS THROUGH TRANSPARENCY

There’s no such thing as a “good time” to get sick or have a health emergency.

One week after my 29th birthday, I suffered a massive seizure and was rushed to the emergency department. Scans showed I had a mass in my brain. After a 9-hour brain surgery, it was discovered I had a grade II astrocytoma, a slow-growing but malignant brain tumor. A few months after the first surgery my tumor grew back, sending me into a whirlwind of treatments over the following years, including a second brain surgery and 24 months of chemotherapy. To say I “had a few questions” about my new health status is an understatement.

Having been born on the cusp between Generation X and the Millennials, my instinctual response as a patient is to Google every new medical term I encounter. For the most part I find what I am looking for, and if I get confused I email my doctor to ask questions. But this makes me wonder, how do people with no formal training in medicine seek answers when we aren’t with our doctors 24/7? Are we all relying on Dr. Google? Are we finding the right answers in our internet search? Or perhaps, more importantly, are we even asking the right questions?

I have friends dealing with sick kids, caring for aging parents, or wondering if and when their family history of breast cancer is going to catch up with them. The modern patient living with chronic illness spends only a few hours each year in health care but over 5,000 waking hours in self-care.10 It’s no wonder that of the 40,000 Google searches happening every second, 2,000 are health-related.11

In early 2017, a change in my health insurance plan forced me to obtain my medical record and transfer it to new doctors. I was given a DVD with my record on it. When I popped the disc into my computer I had no idea this simple action would forever change the way I view access to my health information. There I found a 4,836-page file detailing my previous 8 years of living with brain cancer, including my doctors’ notes.

Like most people, I didn’t know clinical notes were a thing, let alone imagine I could have access to this information. For the previous 8 years, I could Google my condition, but I was never able to read what my own doctors wrote about me. Seeing my doctors’ notes was eye opening and helped fill in details I missed when I was unconscious from seizures and surgeries—moments I thought would forever remain a mystery to me.

Yes, my notes contained a few typos and a lot of medical jargon. Yes, I could tell physicians had copied and pasted from note to note. But I didn’t care about all that because what I also saw was detailed information about my diagnosis and me, and I saw that my doctors cared. To a patient, notes are a behind-the-scenes look at our health. Beyond gaining a greater understanding of my care and my condition, I could tell my doctors and nurses were paying attention and noticing the smallest details about me. This is not something I could ever learn from a Google search.

I got great care from my previous health system—the fact I am here proves that. But it makes me wonder even more: Why hide my notes?

Be There for When Your Patients Are Ready to Engage

Most discussions about health care transformation include strategies to improve patient engagement. I believe two things are fundamental to achieving successful engagement: (1) truly inviting patients to the table and (2) giving us access to information.

I don’t need to tell you that a cancer diagnosis is scary. Access to the medical record isn’t going to change that, but it can help us gain a solid understanding of our condition, a better understanding of our treatment plans, and greater trust in our care teams.12 Research shows that patients forget much of what doctors tell them, up to 80% when the news is bad. Why keep notes from any patient?

Today there is a growing movement toward transparency in health care, a movement in which clinicians and patients are working together to make it easier for regular people like me to have complete access to our full medical records, including our notes. Researchers at OpenNotes and other institutions are studying the effects of sharing clinical notes with patients. The findings are positive and consistent.

When patients read notes, they become more actively involved with their health, ask better questions, and are able to make more informed decisions. And when patients have an opportunity to review their medical information they’re more likely to confirm and remember next steps (e.g., booking necessary follow-up appointments and tests), and can partner in the safety of their own care by identifying errors and inaccuracies in the record.13

Patients care about their own notes more than anyone else, or, as Podge Reed, a double-lung recipient at Johns Hopkins, said, “OpenNotes is a very critical part of my care so that I can ensure that I’m staying on line with my treatment plan and can continue to live a productive life.”

Today, more than 100 health systems across the country are sharing notes through online patient portals. That means over 20 million people can review their notes, online, whenever they choose ... except for me and about 94% of the rest of America. We’re moving in the right direction, but there’s still a long way to go.

Open Notes in Cancer Care

MD Anderson was one of the first health systems to start sharing notes with patients, in 2009, and they have the most experience sharing oncology notes. Not only does MD
Anderson report nothing bad ever happening as a result, the feedback from patients and clinicians about sharing notes has been good. As a result, patients who read oncology notes report benefits similar to those of primary care.

Continued observation of open notes at cancer centers shows that patients who access their electronic records are more informed about their care plan and ask more focused questions. Other cancer centers noted for their implementation of open notes include Cleveland Clinic, Mayo Clinic, Stanford Health Care, and UW Medicine.

But What About Imaging?
The most consistent concern I’ve heard from oncologists about open notes is related to imaging. Some oncologists have had the unfortunate experience of hearing from patients who have seen the results of an unfavorable report before the oncologist was able to talk with the patient. Understandably, a report identifying every possible diagnosis, or a scan showing a growth or return of cancer, can induce anxiety, but it is even worse when presented without the context and empathy a good cancer doctor and good notes can provide.

As a patient and proponent for open notes, I share the same concerns. But open notes, laboratory reports, and/or imaging findings are not an “all or nothing” concept. I have had the opportunity to talk with some of the nation’s top health information technology specialists about open notes, and nearly every feature that makes notes-sharing a possibility can be tweaked on the backend of the electronic health record. It is possible to customize the timing of how and when laboratory and imaging reports are delivered to patients. Some health systems choose to delay the delivery of imaging reports by 3 to 7 days after the report is signed by a radiologist.

Everything can be customized—so don’t let technology be the barrier.

Notes Are Forever
A visit with my oncologist might last 45 minutes, but my note lasts forever. If I had had access to my notes during active treatment, I know I would have read each one with care. A cancer diagnosis fills our lives with uncertainty, but a physician’s assessment and plan provides a roadmap to what’s next. Remove the barriers. Let patients know the notes exist, and invite us in. Make it easy to find the notes and easier for us to be engaged.

I can’t believe it took a massive medical records request for me to have stumbled across my notes, and there isn’t a single thing in my notes I don’t understand. I wish I could have seen them sooner. Your patients are hungry for information, and we can handle it. Although you cannot make patients engage, you can be there when we are ready.

SPIRITUALITY IN ONCOLOGY
Spirituality and religion are important to patients facing cancer, particularly those with advanced disease. Spirituality and religion can be a tremendous source of comfort, strength, and support; however, cancer can also raise or magnify spiritual concerns related to mortality, suffering, meaning, and purpose in life. Although oncologists are seldom trained in spiritual matters, few professionals interact more frequently or intimately with patients as they grapple with these issues. Many clinicians feel uncomfortable when spiritual concerns arise; however, appreciating the deeper dimensions of our patients’ cancer experience, and addressing these issues on a basic level, can benefit both patients and our relationships.

Spirituality and the Religious Landscape of the United States
Spirituality is often thought of as a religious process concerned with promoting connection to God or the sacred; however, it is increasingly recognized that the construct of spirituality is not necessarily rooted in religious faith. The European Association for Palliative Care defines spirituality as “the dynamic aspect of human life that relates to the way persons (individual and community) experience, express and/or seek meaning, purpose, transcendence, and the way they connect to the moment, to self, to others, to nature, to the significant and/or the sacred. Spirituality is expressed through beliefs, values, traditions and practices.” Through this lens, it becomes clear that many familiar patient concerns are by nature spiritual, including questions of meaning (“Why is this happening to me?”), value (“I don’t want to become a burden”), and relationship (“I regret things I’ve said and done”).

This broad understanding of spirituality is particularly important as U.S. religious landscapes shift. According to a 2013 Pew Center survey, more than 20% of the US population identifies with no specific religious tradition, with rates approaching 40% among younger adults. Most patients, even those who are not religious, have systems of belief that bring meaning and purpose to their lives. These formal or informal belief systems can be an important source of support or can be substantively shaken by a cancer diagnosis.

Relevance of Religion and Spirituality to Cancer Care
Cancer is a major threat to people’s sense of identity. Cancer interrupts the trajectory of patients’ lives; it upends a sense of security, raises questions about meaning and purpose, and challenges relationships. For many, religion and/or spirituality can help confront and make sense of this upheaval. Indeed, faith is one of the most important and frequent coping strategies cited by patients. But just as often, the upheavals caused by cancer can challenge the core of patients’ spiritual and religious beliefs. Most patients with cancer experience spiritual needs or struggles, ranging from existential to highly religious in nature. Upward of 75% of patients with cancer, whether religious or not, endorse spiritual struggles, including loss of hope or meaning, the need for forgiveness, and even feeling abandoned, punished, or unloved by God.

Although these struggles do not always present themselves on the surface of clinical encounters, they can be a
powerful undercurrent eroding patients’ well-being and quality of life. Spiritual/existential well-being has been shown to be a powerful predictor of quality of life, over and above physical, emotional, functional, and social well-being.\textsuperscript{25,26} Given the incontrovertible importance of quality of life, it could be argued that care teams should pay much more attention to spiritual well-being.

Religious and spiritual factors can also affect highly personal care decisions,\textsuperscript{27} such as the decision to pursue experimental treatment\textsuperscript{28} or to choose comfort-oriented or intensive care at the end of life. One study found that patients with cancer who relied highly on religion to cope were more likely to receive intensive medical care at the end of life,\textsuperscript{29} potentially reflecting hope for miraculous healing or beliefs about the sanctity of life. It should be emphasized, however, that religion and spirituality operate in highly individualized ways in patients’ medical decisions. In a secular medical environment, patients are often ill equipped to bring deeply held religious convictions to medical decision-making. In these cases, board-certified chaplains or patients’ own clergy can be useful partners in challenging treatment discussions.\textsuperscript{30}

One could argue that religion and spirituality are relevant to cancer care simply because of their importance to patients. Particularly near the end of life, spiritual issues are at the forefront of patients’ and families’ priorities. In one survey of nearly 2,000 terminally ill patients and family members, freedom from pain and peace with God were equally ranked as the most important factors in determining a “good death.”\textsuperscript{31} In fact, spiritual care has long been considered a core domain of quality palliative care and was engrained within the ethos of the modern hospice movement.\textsuperscript{21}

### Patient Perspectives on Addressing Religious/Spiritual Issues Within Cancer Care

Patients’ attitudes toward addressing spiritual issues within clinical care vary according to the patient, the situation, and

<table>
<thead>
<tr>
<th>Tool</th>
<th>Domain</th>
<th>Sample Questions</th>
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<tbody>
<tr>
<td>FICA</td>
<td>Faith</td>
<td>Do you consider yourself spiritual or religious? Do you have spiritual beliefs that help you cope with [contextualize to situation]?</td>
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<tr>
<td>Importance</td>
<td>Importance</td>
<td>What importance does spirituality have in your life? Does it influence your medical decisions?</td>
</tr>
<tr>
<td>Community</td>
<td>Community</td>
<td>Are you part of a spiritual community? Is this a support to you?</td>
</tr>
<tr>
<td>Address within care</td>
<td>Address within care</td>
<td>How would you like me to address these issue in your care?</td>
</tr>
<tr>
<td>HOPE</td>
<td>Source of hope, meaning, comfort, strength, peace</td>
<td>What are our sources of hope, strength, comfort and peace? What do you hold onto during difficult times? For some, spiritual beliefs are a source of comfort. Is this true for you?</td>
</tr>
<tr>
<td>Organized religion</td>
<td>Organized religion</td>
<td>Are you part of an organized religious or spiritual community? What aspects of your religion are helpful or not-so helpful to you?</td>
</tr>
<tr>
<td>Personal spirituality and Practices</td>
<td>Personal spirituality and Practices</td>
<td>Do you have personal spiritual beliefs? What aspects of spirituality or spiritual practices do you find most helpful?</td>
</tr>
<tr>
<td>Effects on care</td>
<td>Effects on care</td>
<td>Has being sick affected your ability to do things that usually help you spiritually? How do your beliefs affect the kind of care you would like me to provide?</td>
</tr>
<tr>
<td>FACT</td>
<td>Faith and/or beliefs</td>
<td>Do you consider yourself spiritual or religious? What things do you believe that give your life meaning and purpose?</td>
</tr>
<tr>
<td>Active</td>
<td>Active</td>
<td>Are you active in your faith community?</td>
</tr>
<tr>
<td>Coping, Comfort, Conflict, Concern</td>
<td>Coping, Comfort, Conflict, Concern</td>
<td>Do your beliefs (faith) help you cope? How has your faith provided comfort in light of your cancer?</td>
</tr>
<tr>
<td>Treatment Plan</td>
<td>Treatment Plan</td>
<td>Based on responses, make a plan to support/encourage, reassess, or refer to a spiritual care provider such as a chaplain or clergy.</td>
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<tr>
<th>Sample One- or Two-Item Spiritual Screening Questions</th>
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<tr>
<td>You’re dealing with a lot. What helps you cope in difficult times? Is spirituality or religion a part of that?</td>
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<tr>
<td>Where do you find strength during difficult times? Do your personal beliefs help you make sense of your illness</td>
<td></td>
</tr>
<tr>
<td>How often are you at peace at the end of the day?</td>
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**TABLE 1. Spiritual Screening Tools**
the type of spiritual interaction. Given the life-threatening nature of cancer and the close relationships between patients and providers, it is not surprising that patients with cancer are particularly welcoming of spiritual conversations with their doctors and nurses. Even among secular urban populations, most patients with cancer believe it is appropriate for oncologists to inquire about their spiritual needs. Another study found that large majorities of patients with cancer approved of oncology doctors and nurses routinely addressing spiritual issues, including asking about spiritual/religious background, referring to chaplaincy, and even offering prayer in appropriate circumstances. Nearly 80% of patients thought that routine spiritual care would have a positive impact on patients. In open-ended responses, patients noted that they thought spiritual care would provide emotional support, help providers see them as “whole persons,” and deepen relationships. Unfortunately, patients seldom experience spiritual care from their cancer care team.

Practical Suggestions

Addressing spiritual or religious issues within clinical care must begin with humility and self-awareness. Clinicians must be conscious of their own belief systems, biases, competence, and boundaries. Discussions must be predicated on respect for patient autonomy, recognizing that our role as clinicians is to listen and support patients within their own belief system, not persuade them toward our own. This aligns with qualitative data showing that patients’ interest in spiritual care arises mainly from a desire to be more deeply heard, understood, and supported by their providers. In contrast, patients generally do not expect or want spiritual counsel from clinicians.

Many patients do not spontaneously bring up spiritual issues with their care team, as culture or past experiences may suggest that doctors and nurses are not interested. To reset these expectations, it is important to create an environment in which patients feel comfortable bringing up spiritual issues, if and when they choose. An easy starting point is to pay attention and respond to patients’ own cues, including statements like “So many people are praying for us,” “We are trusting God for...,” and the presence of scriptures or religious cards in a hospital room. Research shows that clinicians rarely acknowledge or respond to types of spiritual statements, effectively telling patients we are uninterested. Although there are no simple formulas on how to respond to spiritual cues, it can be helpful to approach these observations with a respectful curiosity. We suggest using open-ended questions, such as “It sounds like your faith community is very important to you, tell me more about that” or “I’m really interested in what you mean by that. Would you mind sharing more?” These conversations can be very short, but they send a signal to patients and grant permission for future open conversations about the spiritual dimensions of their experience.

Another important practice is taking a “spiritual history,” which refers to asking patients about their spiritual background, beliefs, and support system. This need not be at the first clinical encounter and is likely most appropriate after several visits when a relationship exists. A variety of spiritual history tools have been developed, including FICA, HOPE and FACT, which are detailed in (Table 1). Rather than use a formal spiritual history tool, it may feel more natural to ask one or two open-ended questions. Examples include “You’ve been dealing with a lot lately. What helps you cope in difficult times? Is spirituality or religion a part of that?” or “Where do you find strength during difficult times?” or “How often are you at peace at the end of the day?” Regardless of the tool, it is probably most important to try out different words and phrases and use what works for your own communication style.

If patients bring up specific spiritual struggles, be mindful that our job is not to “fix” the problem. Most important is to listen well, to empathize, and to offer a caring and non-judgmental presence. Detailed discussion of responding to spiritual needs is beyond the scope of this review, but it can be helpful to follow communication principles, such as the NURSE framework for responding to emotion: Naming, Understanding, Respecting, Supporting, and Exploring. When patients get stuck in unanswerable questions (e.g., “Why is this happening to me?”) or if they express spiritual pain (“God is punishing me”), acknowledge and listen to patients’ concerns. Then, validate the importance of their struggle and ask permission to involve spiritual professionals, such as a board-certified chaplain or patients’ own clergy. Debriefing with professional spiritual care providers can be an important way to build comfort and skills in integrating spiritual care within the clinical care of patients.

References


Telemedicine in Cancer Care

S. Joseph Sirintrapun, MD, FASCP, FCAP, and Ana Maria Lopez, MD, MPH, FACP

OVERVIEW

Telemedicine uses telecommunications technology as a tool to deliver health care to populations with limited access to care. Telemedicine has been tested in multiple clinical settings, demonstrating at least equivalency to in-person care and high levels of patient and health professional satisfaction. Teleoncology has been demonstrated to improve access to care and decrease health care costs. Teleconsultations may take place in a synchronous, asynchronous, or blended format. Examples of successful teleoncology applications include cancer telegenetics, bundling of cancer-related teleapplications, remote chemotherapy supervision, symptom management, survivorship care, palliative care, and approaches to increase access to cancer clinical trials. Telepathology is critical to cancer care and may be accomplished synchronously and asynchronously for both cytology and tissue diagnoses. Mobile applications support symptom management, lifestyle modification, and medication adherence as a tool for home-based care. Telemedicine can support the oncologist with access to interactive tele-education. Teleoncology practice should maintain in-person professional standards, including documentation integrated into the patient's electronic health record. Telemedicine training is essential to facilitate rapport, maximize engagement, and conduct an accurate virtual exam. With the appropriate attachments, the only limitation to the virtual exam is palpation. The national telehealth resource centers can provide interested clinicians with the latest information on telemedicine reimbursement, parity, and practice. To experience the gains of teleoncology, appropriate training, education, as well as paying close attention to gaps, such as those inherent in the digital divide, are essential.

Telemedicine uses telecommunications technology as a tool to deliver health care to populations with limited access to care.1 Initially developed to assist in the care of astronauts in space, telemedicine technology was soon being adapted and studied to increase access to care for populations on Earth.2 Since the demonstration projects in the 1970s, access to telemedicine technology has expanded with greater portability, improved usability, lower costs, and higher quality. From the National Aeronautics and Space Administration’s singular STARPAHC Project to the myriad of small, large, freestanding, academic, commercial, direct-to-consumer telemedicine services available in the United States today, telemedicine has been tested in multiple clinical settings. Most studies demonstrate at least equivalency to in-person care and high levels of patient and health professional satisfaction.3,4 Some studies demonstrate improved outcomes compared with in-person care.5 These factors have fueled ongoing interest in improving health care delivery by integrating teleconsultations with traditional in-person clinical care.

TELEMEDICINE

Definitions and History

Approach. Telemedicine services may use a variety of telecommunications technology to support clinical care. There are two primary approaches to telemedicine services: synchronous or asynchronous format. The patient and consultant may engage virtually and synchronously or asynchronously. The former uses fully interactive video technology in real time. The latter stores and forward or transmits clinical data elements, such as medical reports, images, and video recordings, to be interpreted at a later time. This latter approach is known as “store-forward.” Telemedicine services, including teleoncology, may use one or both of these formats with or without intermittent in-person consultations based on clinical needs. The physical exam may be accomplished virtually, with the exception of palpation, and/or data may be gathered by the local clinician and relayed to the teleconsultant or teleoncologist. Given the skills necessary for teleconsultation, team-based health professional education regarding the delivery of telemedicine services is essential for the teleconsultation team. Patient education and orientation regarding telemedicine and what to expect promote patient-centered care and engagement.6

TELEONCOLOGY

Rationale

The predicted shortage of oncologists in the United States,7 the greying of the population,8 and the well-documented oncology health care work force and population geographic...
mismatch provide specific rationale for implementation and expansion of teleoncology services. Telemedicine technology can serve to redistribute the oncology work force in a rational way, where needed. The convenience of teleoncology may serve to minimize the disruption that the disease can cause.

Examples of Effective Teleoncology Interventions
Multiple aspects of teleoncology care have been studied. As an initial step, the technology was explored in real-time video format to increase access to oncology care in rural populations where the prior standard was for the oncologist and/or the oncology team to travel to the rural site. Doolittle and colleagues from the University of Kansas Medical Center demonstrated both clinical and cost effectiveness of this approach. Since then, others have confirmed the efficacy of this approach and identified high levels of patient satisfaction and improved access to clinical cancer services.

Increased use of telemedicine is associated with improved cost efficacy. Bundling of Services
Because quality care of the patient with cancer requires multidisciplinary team–based care, telecommunications technology can support interprofessional care. Teleoncology lends itself well to bundling of services. At its simplest, most teleoncology visits are a blend of real-time and store-forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward with the direct patient interaction taking place as a real-time videoconferencing session and with transmission forward.

Building on this experience, Lopez et al and Weinstein et al demonstrated the efficacy of bundling of teleradiology, telepathology, and teleoncology in breast cancer care, as had previously been accomplished for telediabetes care, to allow for enhanced access to quality care as a blend of in-person care (i.e., the clinical services available on site) and teleconsultative care.

Telegenetics for Cancer Care
Building on the experience with telegenetics in pediatric populations, the Arizona Telemedicine Program and others began providing telegenetic services to urban and rural populations. The strong literature on phone consultations for genetics care provided a sound rationale for expansion to telediabetes services. The approach successfully identifies genetic carriers and yields high levels of patient satisfaction.

Most Recent Innovations
Teleoncology services are exploring remote supervision of chemotherapy delivery. Limitations include physical exam assessment, which may be fully accomplished virtually with the exception of palpation. Training in the virtual physical exam is essential for success. Collaboration and communication with the referring clinician regarding physical exam findings can address the inability to palpate. Some programs rely fully on the local physical exam. Portable, home-based, and mobile technologies may be used for home health follow-up that may include wound care, symptom management, and palliative care (see Mobile Applications for Cancer Care section below).

Cancer Clinical Trials
Access to cancer clinical trials is often limited for patients living in nonurban areas. Even if patients are not traveling long distances for cancer care, the additional time requirements associated with cancer clinical trial enrollment can be a deterrent for participation. Telemedicine may be used to facilitate access to cancer clinical trials by facilitating trial eligibility assessment, consent, participation, and cancer clinical trial follow-up, including symptom assessment and management.

PRACTICAL APPLICATIONS

- Telemedicine is the use of telecommunications technology to deliver health care to populations with limited access to care.
- Telemedicine has generally been demonstrated to be at least equivalent to in-person care, improve access, and decrease costs with high levels of patient and health professional satisfaction.
- Telemedicine may take place synchronously, asynchronously, or blended in-person care.
- The patient and the consultant may engage virtually via fully interactive video technology in real time or asynchronously by storing and forwarding clinical data elements, such as medical reports, images, and video recordings, to be interpreted at a later time.
- Effective teleoncology interventions include cancer telegenetics, telepathology, bundling of cancer related teleapplications, remote chemotherapy supervision, symptom management, survivorship care, palliative care, and approaches to increase access to cancer clinical trials, some of which may use mobile technologies.
- The national telehealth resource centers can provide interested clinicians with the latest information on telemedicine reimbursement, parity, and practice.
Attaining accurate diagnoses and tissue sufficiency for molecular studies highlights the importance of ROSE in providing immediate feedback on triaging specimens obtained through minimally invasive procedures.

ROSE is traditionally performed by pathologists or cytotechnologists who must go on site where the procedure is performed. The number of ROSE procedures delivered is limited by the number of available cytotechnologists and pathologists to go on site. Some on-site locations lack available cytotechnologists and pathologists. With hard cases, time spent performing ROSE can extend to hours if the lesion is near inaccessible. The time expended on such cases creates an opportunity cost of availability. Pathologists or cytotechnologists caught up with such demanding procedures are no longer available for other procedures. Because of the immediacy of ROSE, synchronous real-time telecytology (TC) addresses all of those issues.

Rationale
Memorial Sloan Kettering Cancer Center (MSKCC) has developed two large-scale models for synchronous real-time TC operations for ROSE. The first model addressed our on-site satellite locations, which lack available cytotechnologists and pathologists. MSKCC had established multiple satellite locations offering interventional radiology and endoscopy services. The volume of procedures, however, was not able to justify the physical on-site presence of a cytotechnologist. The solution created is TC through robotic microscopes.

The second model addressed more centrally located high-volume locations that have available cytotechnologists and pathologists. The solution created is TC through streaming high-definition video microscopy. This framework for TC enabled for more efficient use of skilled resources to render ROSE.

Approach
In the first model for synchronous real-time TC, cytotechnologists off site control robotic microscopes deployed to the satellite sites. Through a multidisciplinary effort of education and training, teams in laboratory medicine, interventional radiology, and endoscopy prepare the cytologic specimens through staining and loading of the robotic microscopes. Cytotechnologists are then able to control the robotic microscopes and communicate the results back to the on-site procedural teams.

In the second model for synchronous real-time TC, cytotechnologists go to multiple on-site locations and leverage streaming high-definition video microscopy technology. Cytotechnologists and fellows go on site to prepare the cytologic specimens and drive the glass slides on the microscopes to selected critical regions of interest. The images, in turn, are streamed back to a cytopathologist centrally. The cytopathologist essentially validates and coordinates a distributed team of cytotechnologists via TC. Through this TC framework, a more efficient workflow is established to increase the scale and coverage of all incoming ROSE requests.

Assessment
In the first model for synchronous real-time TC using robotic microscopes, over 22 months, 439 showed a perfect correlation of 92.7% (407 out of 439) of the cases. An adequacy upgrade (inadequate specimen becomes adequate) occurred in 6.6% (29 out of 439) of the cases. In an adequacy downgrade (adequate specimen becomes inadequate), the most relevant metric is near zero at 0.7% (3 out of 439) of the cases.

In the second model for synchronous real-time TC using streaming high-definition video microscopy, over 26 months, 12,949 cases showed a perfect correlation of 93.0% (12,043 out of 12,949). An adequacy upgrade (inadequate specimen becomes adequate) occurred in 6.7% (867 out of 12,949). In an adequacy downgrade (adequate specimen becomes inadequate), the most relevant metric is near zero at 0.3% (39).

Both TC models show adequacy downgrades (adequate specimen becomes inadequate) at a minimum. Adequacy downgrades are critical metrics because preliminary adequacy assessments incorrectly designated as adequate lead to premature finalizing of procedures without the accurate sampling of lesions. Adequacy downgrades result in either delay of diagnoses or need for repeat procedures.

Future Directions
ROSE is a successful use case of telepathology at our institution. With that success, our entire operation of cytologic preparations for ROSE is now entirely driven by TC. Furthermore, to our knowledge, our institution has the most extensive use of TC in the world.

ROSE TC illustrates one example of the value of synchronous telepathology. Implementation is now underway at our institution on an ambitious large-scale asynchronous telepathology initiative to render secondary opinions through digital slide-scanning technologies. Termin the pathology consultation portal, health care entities will be able to upload digitally scanned images of glass slides to receive secondary opinions for diagnosis. The immediacy and availability of such a portal will disrupt how pathology consultation is performed today by obviating the need for physical transport and manual handling of glass slides and patient information. International institutions will likely see the most benefit. There are savings in time by overcoming the barriers of long durations for physical transportation, and there is the circumvention of regulatory restrictions by some countries in not allowing glass slides to be sent outside their borders. Such technology expands the accessibility to anyone who desires a second pathology consultation.

MOBILE APPLICATIONS FOR CANCER CARE
Mobile health, or mHealth, is rapidly emerging as a critical tool for cancer care from prevention to palliation. Recognizing that patients with cancer seek to stay well and limit time in the outpatient and inpatient medical settings, mHealth’s goal is to help patients stay well while staying closer to home and living their lives. Portable, home-based,
and mobile technologies may be used for home health follow-up that may include wound care, symptom management, and palliative care.

Wearable technologies can provide intermittent or continuous monitoring of vital signs. Temperature may be assessed continuously or intermittently through skin sensors that may provide early clues to neutropenic fever. Weight assessments may take place intermittently with results transmitted directly to the clinical team.

Often linked to smartphone applications, mHealth technologies may broadly include texting and messaging efforts that provide patients with ongoing engagement, support, and coaching. Smartphone applications have been developed to support lifestyle modification, wellness activities, and medication adherence. These assistive technologies may also target specific populations, such as the aging. Smartphone applications have been developed to support lifestyle modification, wellness activities, and medication adherence. These assistive technologies may also target specific populations, such as the aging. Attachments to smartphones can provide the clinician with tools to assist with patient care. These interventions range from iPad-based group therapy visits for young adults with cancer to the use of smartphone digital images to assess the cervix after abnormal screening.

POLICY AND IMPLEMENTATION EFFORTS ESSENTIAL FOR TELEONCOLOGY CARE

When to Consider Teleoncology

If your practice is providing care to sites that are requiring considerable travel time, you may wish to consider a virtual solution. The saving of travel time may decrease your stress while supporting clinical productivity and well-being. The factors to consider are distance between the referring site and consulting site, frequency of travel, the savings in travel time for the clinical team and the patient/family, the service need, and your capacity to meet the need. Although the initial costs may seem high, remember that the more frequently the system is used, the lower the costs are per session.

Practice Factors

Teleoncology practice should maintain in-person professional standards, including supporting full documentation that is integrated into the patient’s electronic health record. With improvements in technology, depreciation, and cost efficiencies, using the best technology that you can afford will keep your practice closer to the leading edge as technology evolves. As you develop teleoncology clinical processes, consider your existing in-person processes. Developing similar processes will facilitate use, minimize errors, and improve patient care.

Training

Because few practicing physicians are familiar with telemedicine technology, training is essential. A teleconsultation is not simply FaceTime with a patient. Training with the telemedicine technology is essential to facilitate rapport, maximize engagement, and conduct an accurate virtual exam. With the appropriate attachments, the only limitation to the virtual exam is palpation.

Reimbursement

Telemedicine reimbursement is not uniform across the country and remains a barrier to wider clinical implementation. Reimbursement may serve as either a deterrent or a facilitator depending on your state. It is important to explore and learn the rules in your own state.

For example, Medicare considers where the patient is located (that is, where the teleconsultation is originating) in its reimbursement decision. Patients located in a health professional shortage area are more likely to have teleconsultations covered by Medicare. Health professional shortage areas may include critical access hospitals, rural health clinics, and federally qualified health centers. Although the teleconsultant bills for the consultation, the originating site may bill a facility fee. The latter may require the presence of a health professional at the originating site. Each state’s Medicaid requirements may differ. Become familiar with your own state requirements regarding services covered, clinicians covered, and any specific documentation that may need to be specified in the progress note. Always check the patient’s own insurance regulations. Even though some payers, especially large payers, may cover telemedicine services, the patient’s own insurance plan may not.

Some states have enacted telemedicine parity. Please see the American Telemedicine Association’s website for a list of the states that have passed telemedicine parity laws (www.americantelemed.org/policy-page/state-policy-resource-center). Most telemedicine services will require specific codes for reimbursement. It is important to confirm the proper code or modifier to use when billing for medical services. In some states, nonphysician clinicians may also be able to provide reimbursable services. If the clinician chooses to bypass insurance coverage and bill the patient directly, the patient may need to sign a waiver.

The national telehealth resource centers can provide interested clinicians with the latest information on telemedicine reimbursement (www.telehealthresourcecenter.org).

Tele-education

Telemedicine can also serve to support the oncologist in the rural area by supporting access to tele-education, camaraderie, and support. Using technology for distance education is well established. Similar to the clinical experience, education may be synchronous, asynchronous, or blended. To support camaraderie, blended or synchronous approaches may be most effective. A blended educational program may include viewing of a recorded session, followed by an interactive question-and-answer session. Educational support is not only needed in rural or remote areas. With the ever-changing landscape of care, tele-education may serve the essential function of helping to build and support the oncology workforce in both urban and rural settings and in multidisciplinary settings (e.g., oncology, behavioral health, and primary care) in partnership with interprofessional colleagues (e.g., physicians, nurses, genetic counselors, pharmacologists, and others).
Multidisciplinary and Interprofessional Tumor Boards
Both disease-specific and molecular tumor boards serve to bring together health professionals to review, discuss, and prepare a treatment plan for a patient. Although generally accomplished on site, the technology can be used to bridge distances for some disciplines. For example, the pathology and/or radiology may be “beamed in” with telepathology and teleradiology, respectively. Some tumor boards are considering including the patient and family in the discussion.

FUTURE DIRECTIONS
The potential that technology brings to facilitate care is tremendous. In cancer care, services may be bundled with a blend of in-person and virtual options. Clinicians may be brought together virtually for the benefit of the patient, providing not only the necessary multidisciplinary care but also the necessary interprofessional care. Telecommunications technology enables patients to receive more care at home as the point of care shifts away from the hospital and the medical office. Like other telemedicine interventions, teleoncology is generally found to be equivalent to in-person care and demonstrate costs savings and patient satisfaction.

Barriers to dissemination remain and include technology costs, inconsistent billing and reimbursement regulations, data security risks, and state licensure requirements for clinicians. Although smartphones, internet access, and cell phones are fairly ubiquitous in the United States and globally, as clinicians seeking to provide quality care to all of our patients, we must remember that there is a digital divide related to access and use. The digital divide limits access to these innovations and limits the ability to study and understand the impact of these innovations in some populations—generally, the most vulnerable.

The digitalization of health records holds the promise of better exchange of health information to achieve the right care at the right time for all people. The virtual linking of the electronic health record with diagnostic tools may include portable cameras equipped with secure software to assess skin changes and rashes associated with chemotherapy or radiation, as well as computer-based interactive tools that assess symptoms related to cancer care in real time. These diagnostic tools may be linked to appropriate patient education materials for health education at the point of need. Ultimately, this technology may develop to the point at which the educational materials automatically modify to patient literacy based on speech recognition.

The ability to exchange de-identified health information electronically may yield unprecedented access to population-based data. Discerning which data matter, which difference makes a difference, may ultimately be defined by the linkage of electronic records to artificial intelligence tools that can support clinical decision-making.

The opportunity of big data analytics may soon be evident along the spectrum of health care. As our ability to analyze data and predict outcomes improves, personalized treatment approaches will be uncovered and tested in real time.

Technology is a tool that may free the physician to focus on patient care. We may see improved coordination of cancer care with lower costs, time savings, early disease detection, and increased access to care, education, and individualized care. To see these successes, we must focus on appropriate training, education, and reimbursement as well as paying close attention to gaps such as those inherent in the digital divide.

References


The concept of cancer precision medicine, and that of precision medicine informatics, has always hinged on one key premise: that most cancer therapies are designed for the “average patient” as a “one-size-fits-all” approach. But there is no “average patient,” and thus most treatments will be successful for some patients but not for others. “Precision medicine” should not be conflated with “personalized medicine,” as both terms are sometimes used interchangeably. Precision medicine tailors therapies to classes of patients on the basis of the differences in people’s genes, environments, and lifestyles. Personalized medicine implies customization for an individual patient. Precision medicine simply expands this to the cohort level.1 Taken together, one can think of precision medicine as designed to target the right disease with the right treatment of the right set of patients at the right time.

For precision medicine informatics to be effective, precision medicine requires technology development that allows us to identify key altered pathways that are susceptible to molecularly targeted or immunologic therapies.2 The increasing customization of medical treatment to specific patient characteristics has been possible through continued advances in (1) our understanding of the physiologic mechanisms of disease, leading to the proliferation of omics data (e.g., proteomics, metabolomics), and (2) computing systems (e.g., patient and trial matching algorithms) that facilitate the development and application of targeted agents.3 These advancements allow improved outcomes and reduced exposure to the adverse effects of unnecessary treatment. They can help us better decipher the interpatient (between patients) and intrapatient (different tumors within the same patient) heterogeneity that is often a hurdle to treatment success and can contribute to both treatment failure and drug resistance.4

Precision medicine algorithms and strategies have already borne fruit. The introduction of U.S. Food and Drug Administration (FDA)–approved treatments that are tailored to specific characteristics of individuals, such as a person’s genetic makeup, or the genetic profile of an individual’s tumor have become more routine. Patients with a variety of cancers routinely undergo molecular testing as part of patient care, enabling physicians to select treatments that improve chances of survival and reduce exposure to adverse effects. Importantly, omics-based cancer medicine is here. In 2017,
nearly 50% of the early-stage pipeline assets and 30% of late-stage molecular entities of pharmaceutical companies involved the use of biomarker tests. Furthermore, more than one-third of drug approvals have had DNA-based biomarkers included in their original FDA submissions.

**EXPLOSION OF OMICS-TYPE DATA**

Although genomics data are commonly mentioned in the same breath as precision medicine, it is useful to point out that genomics is simply one type of precision medicine data. Other forms of precision data include, but are not limited to, such things as radiographic features (radiomics), patient-reported outcomes (personomics), and digital pathology. By “genomics data,” we are referring to the ability to interrogate the genome using next-generation sequencing techniques. It is equally important to note that omics-type data can be derived from (1) the tumor, (2) the patient, (3) tissue surrounding the tumor “stroma,” (4) circulating blood, and (5) other bodily fluids. Ongoing research has increased our understanding of the underlying pathophysiology of not only the tumor but also the patient-tumor interaction through these omics data. Acquisition of these omics data has required improvements in detection techniques and data analysis.

As an example, assaying proteins using immunohistochemistry, the use of singular antigens that bind to single proteins of interest in cancer tissue, is now being supplanted by mass spectrometry, which allows massively parallel identification of hundreds of proteins simultaneously. However, it has taken improved computer performance (and supercomputer clusters) to accurately identify this large number of proteins in a reasonable amount of time. This expanding field, proteomics, provides a far more accurate readout compared with immunohistochemistry, which is often subjective and difficult to parallelize. Advanced DNA sequencing, which ushered in the genomic revolution, has also improved greatly. Our ability to perform DNA sequencing with trace amounts of starting material (low-passage reads) with improved fidelity and detection is allowing us to detect circulating tumor DNA from the blood. Circulating tumor DNA is tumor-derived fragmented DNA circulating in blood along with cell-free DNA from other sources, measuring about 150 bp. Circulating tumor DNA provides an overview of the genomic reservoir of different tumor clones and genomic diversity. Circulating tumor DNA may finally provide a means of assaying intrapatient tumor heterogeneity, allowing us to get a sense of the relative abundance of genomic alterations across metastatic deposits within a patient. Other promising omics technologies include metabolite analysis. Metabolites have traditionally been singular molecules detected by immunoassay in the clinic. Metabolomics aims to measure abundances of all small molecules detectable in biospecimens, including blood, tissue, urine, and breath, among others. Typically, mass spectrometry and nuclear magnetic resonance techniques are applied to measure hundreds to thousands of metabolites in a given sample. The chemotherapeutic drug methotrexate, for example, has levels that are detected via immunoassay for quantification purposes. However, immunoassays measure only singular known metabolites, and it is well known that combinations of metabolites are more clinically relevant than singular metabolites.

**CHALLENGES IN UNDERSTANDING OMICS DATA FOR CLINICAL USE**

To use these omics data meaningfully for clinical use requires systems that help clinicians sort through the omics and context and interpretation. Algorithmically, there has been a shift to using informatics methods such as gene signatures and nonlinear approaches such as neural networks and advanced aggregative techniques to model complex relationships among patients to facilitate this process. Importantly, these approaches are the root of cohort matching algorithms that aim to find “patients like my patient.” Results of these algorithms are simpler to understand and have propelled the growth of clinical trials matching algorithms. National trials such as NCI-MATCH that pair patient tumors with specific tumor alterations to targeted medications are a simplistic first step in this paradigm shift. The ability to perform complex matching, and matching rules, has relied on the growth of aggregated patient data sets and the ability to quickly assess tumor omics data. Although not all of these trials have been successful, there is evidence that as a general approach, patients treated with therapies that match the molecular profile of their tumors have better outcomes than those who are not. As more targeted agents become available, the number of laboratories offering molecular testing has increased, and large academic, tertiary care hospitals have begun conducting molecular tumor boards (MTBs) at which experts weigh in on the molecular profile as well as other relevant factors for specific patients to suggest matched therapies. However, the gold standard remains a genomics or domain expert to provide interpretation of the data. Thus, these interpretations are often facilitated by MTBs or by clinical decision support software. But given the shortage of subtype and pathway specific domain expertise, virtual tumor boards (VTBs) are often used to bring disease certain expertise in treatment planning. VTBs are particularly useful for rare tumors, in which domain expertise may be difficult to obtain locally, or

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**PRACTICAL APPLICATIONS**

- Learn about incorporating genomic data into EHRs.
- Understand the role of data-sharing consortia in aggregating data from large numbers of patients.
- Learn about molecular tumor boards, including virtual tumor boards, and other mechanisms for interpreting complex genomic data.
- Learn about data safety and patient privacy as it applies to precision medicine.
- Develop an appreciation for the necessity of incorporating precision medicine–based therapies into routine clinical practice.
in late-stage tumors, in which standard-of-care options have been exhausted and novel treatments are being explored.

**PRECISION ONCOLOGY IN THE COMMUNITY**

**SETTING**

Background

The vast majority of patients with cancer in the United States are treated at community hospitals and practices. It is therefore paramount that precision medicine oncology technologies be available to these facilities. Not only is there a delivery issue, there is a need to encourage the widespread uptake of precision genomics by community oncology practices. This will not only facilitate potentially better patient care but also aid in accruing patients to omics-driven clinical trials. However, considerable challenges exist in implementing a precision medicine program, including administrative, logistic, and financial barriers. Arguably, the most imposing barrier may be the willingness and motivation of oncologists to incorporate routine genomic testing into their daily workflows when the clinical benefit of panel-based omics testing in all tumor types has not been definitively established. Overcoming these substantial obstacles by establishing a comprehensive platform to integrate omics data into clinical practice requires the support and engagement of the key stakeholders in each practice or health care system, which includes oncologists, pathologists, nursing and research staff members, administrators, electronic health records (EHRs), and information technology specialists and others.

As a case example, we use the Swedish Cancer Institute as a didactic means of uncovering and overcoming challenges in bringing a precision medicine program to the community. In September 2014, the Personalized Medicine Research Program was implemented at the Swedish Cancer Institute, a nonuniversity, community-based research practice in Seattle, Washington. The Swedish Cancer Institute is a component of Providence St. Joseph Health, a system comprising 50 hospitals across seven western states. In their model, patients are enrolled into an institutional review board–approved registration protocol, and tumors are profiled using a customized in-house gene alteration panel, originally composed of 68 gene alterations and recently expanded to 79 gene alterations, focused on solid tumors. Data are collected using a cloud-based integrated informatics platform to facilitate evidence-based analysis, clinical trials matching, and an MTB.

The underlying software platform to facilitate management of this clinical and research program has been developed by a third-party vendor, Syapse (San Francisco, CA). Provider acceptance of this technology was enhanced by integrating the platform into the Swedish Medical Center’s existing EHR. This reduced redundancy by pulling in patients’ clinical data directly from previously entered fields within the EHR and from the institution’s cancer registry. Similarly, results of the genomic analysis and recommendations of potentially suitable therapies are delivered to the provider within the EHR and did not require separate logins to an external web portal. Raw profiling data from the gene alteration panel are imported directly from an affiliated Clinical Laboratory Improvement Amendments–certified laboratory, with the additional capability of importing omics data from large commercial genomics test vendors. Subsequent iterations of the platform will integrate and present meaningful outcomes data. Data connections also exist, or are under development, with a clinical trials management system, institutional disease site registries, state and national registries, and the anatomic pathology laboratories. To optimize use of the emerging data set, projects are under way to apply machine learning to develop decision support tools.

Financial barriers continue to be a limitation to more widespread uptake of precision medicine testing, although an early study suggests that it may be a cost-neutral undertaking. Billing for the next-generation sequencing panel in the Personalized Medicine Research Program was submitted to patients’ insurance companies on the basis of medical necessity, and an interim analysis of reimbursement patterns has shown that approximately one-third of patients received reimbursement, with private and Medicare managed care plans reimbursing at the highest frequency and level. The recent FDA approvals of several commercially available NGS panel tests will likely result in greater accessibility to genomic testing. For biomarkers that strongly implicate a well-validated targeted therapy, obtaining the medication is difficult. These medications are designated as "off-label" as they generally do not have an FDA indication for the tumor type in question. Albeit time consuming, many insurance plans increasingly are willing to consider evidence from targeted therapies in the appeals process. Furthermore, many pharmaceutical companies provide copay or compassionate use programs for patients that demonstrate need.

**Targeted Therapy Trials in the Community**

The main goal for setting up the Personalized Medicine Research Program was to provide the ability to match genomic results with appropriate or promising therapies. Therapeutic suggestions, or the domain expertise that is clinically actionable, which may include on-label, off-label, and clinical trial options, are formulated by a molecular decision support service (N-of-One, Concord, MA). A molecular pathologist reviews these suggestions before being included together with the genomic results in the final report. A subset of these cases are discussed, by oncologist or pathologist request, at a biweekly MTB, to provide additional input on interpretation of molecular results. In the first 869 patients enrolled in this protocol, results of the next-generation sequencing testing was found to affect 105 patients (21%), consistent with the impact of molecular profiling in other published series. The MTB has proved to be a key venue for engaging and educating clinicians about precision medicine. Clinical trial enrollment was a key goal of establishing a precision medicine program. In addition to single tumor site–based molecular trials, the current framework also facilitates the recruitment of patients to large national basket trials, including NCI-MATCH (NCT02465060) and ASCO’s Targeted Agent and Profiling Utilization Registry (TAPUR; NCT02693535) trial.
Data-Sharing Consortia
Several initiatives are under way to further leverage genomic and clinical data from the growing percentage of cancer patients who are participating in precision medicine programs across the country. The American Association of Cancer Research initiated Project Genomics Evidence Neoplasia Information Exchange (GENIE), a multiphase, multi-year, international data-sharing project to assist in clinical decision-making in rare cancers, and in rare variants of common cancers. Research outcomes for Project GENIE are (1) identification of novel therapeutic targets, (2) aiding in the design of biomarker-driven clinical trials, and (3) identification of genomic determinants of response to therapy. In the first phase of the project, the eight founding international academic institutions released a 19,000-patient data set.21 Notable findings from the initial GENIE data demonstrate that almost all tumor types, especially carcinomas of unknown primary, have at least some samples with a high mutational burden, defined as mutation burden above the 90th percentile of all samples tested on the larger sequencing panels (12.3 mutations/Mb). This finding suggests that the strategy of checkpoint inhibition may be relevant to a proportion of patients in a wide variety of cancer types.22 As of early 2018, both the Swedish Cancer Institute and the Providence Portland Cancer Center’s Earle A. Chiles Research Institute, both institutes within Providence St. Joseph Health, have become participants in Project GENIE. This represents an important contribution to the GENIE data set from a large community-based health system.

Along similar lines, the Oncology Precision Network consortium was launched to share deidentified aggregated omics data among multiple community and academic institutions.23 Founding members of the consortium include Intermountain Healthcare (Salt Lake City, UT), the Swedish Cancer Institute, the Providence Portland Cancer Center, and the Stanford Cancer Institute (Stanford, CA), with the Syapse platform facilitating the data sharing. This consortium anticipates sharing genomic and outcomes data from more than 100,000 patients, representing more than 200 hospitals, annually by 2019, with mostly large community-based hospital systems, and some additional academic centers, having committed to joining the Oncology Precision Network. All contributing partner sites will be able to access the data, which are appropriately deidentified and Health Insurance Portability and Accountability Act and Health Information Technology for Economic and Clinical Health compliant, in real time and will allow treating physicians to view real-world outcomes for other patients with similar omics profiles.

GROWTH OF VIRTUAL TUMOR BOARDS
Background
As mentioned earlier, although molecular profiling and tumor board discussion are available to patients at many large academic hospitals, 95% of patients with cancer are treated at the community level. The Swedish experience provided one such example of using decision support software to provide a level of genomic interpretation. There are other growing approaches. One such effort involved was initiated in the pancreatic cancer domain and involves academic medical centers, patient advocacy groups, community hospitals, and a small company to develop a scalable VTB. A scalable VTB can take advantage of cloud-based computing, mobile device engagement, and collaborative platform software development. The rapid pace of publication of new results describing biomarker-drug interactions relevant to cancer makes it difficult for most oncologists to stay up to date. In addition, the presence of multiple actionable biomarkers in a single tumor can present challenges for physicians in that a strong informatics system becomes necessary when confronted with the huge number of potential combination therapies in clinical trials. A VTB can bring together all this information, along with patients’ clinical and molecular data, to the fingertips of clinicians using a single web-based portal. Other cancer domains and their respective oncologists who run MTBs at academic and commercial organizations are now adopting this VTB model.

Use of a Virtual Tumor Board by the Pancreatic Cancer Action Network’s Know Your Tumor Program
The creation of the aforementioned pancreatic VTB example is described in better detail here. A multidisciplinary team of clinicians and informaticians from the Pancreatic Cancer Action Network, Perthera, and Georgetown University’s Lombardi Cancer Center orchestrated a precision medicine operation called Know Your Tumor in which 640 patients with pancreatic cancer referred from 287 community and academic centers in the United States were enrolled into the largest geographically distributed precision medicine program for pancreatic cancer. A VTB consisting of more than 10 oncologists reviewed each case and identified highly actionable findings in 27% of patients, including 15% of patients with homologous recombination-deficient tumors. An additional 27% of patient samples also carried molecular abnormalities, the targeting of which would alter therapeutic choices. In all, more than 50% of patient samples were actionable or highly actionable. These patients were followed longitudinally, and at the time of data cutoff, 24% of the patients (156 patients) had initiated new therapy, 81% (126 patients) of whom used therapies that matched their molecular profiles. These data and analysis of the VTB were quantitative in nature and required the informatics teams to collect and curate the data, which were received mostly in nonstandard formats. VTBs provide a unique opportunity to automate this process with a web-based, asynchronous, VTB with highly usable interfaces for clinicians, who are overburdened at most academic medical centers and worse so in community clinics.

Technical Implementation of Virtual Tumor Boards
VTBs have their own set of technical challenges aside from simply coordinating health care providers. The VTB process of delivering patient reports has guided its development. To date, the many features of this pancreatic VTB include the following:
• An information technology infrastructure consisting of databases for multiple types of information to feed into the VTB: patient history, molecular profiling data, and external knowledge of biomarkers, drugs, and clinical trials.

• A treatment scoring system (Fig. 1) used to rank single-agent and combination therapies on the basis of the strength of molecular biomarkers, the activity of the drug(s) in the specific cancer type, and prior exposure of the patient to the drug under consideration (or drugs with similar mechanisms of action). In the VTB example above, the scoring model is based on best practices published by the ClinGen Somatic Working Group,24 Association of Molecular Pathologists,25 and OncoKB.26

• A user interface consisting of (1) a chat feature allowing asynchronous discussion of a case, thus avoiding scheduling conflicts for geographically dispersed oncologists; (2) a single-tab view allowing access to patient-related documents such as medical history, laboratory results, and reports all in one place without having to navigate away from the tab; (3) resources and references allowing access to external databases within the VTB (example databases include National Cancer Institute cancer dictionaries, clinical trials database, PubMed and Online Mendelian Inheritance in Man) with the intent that the user does not have to leave the VTB interface to access critical information from other references databases; and (4) a case-tracking feature allowing clinicians to know whether a case is ready for analysis or is awaiting laboratory results or medical history.

• Data sources including Knowledgebase, Molecular DB, and Patient EHR DB, described below.

Precision Medicine Sources for Computerized Virtual Tumor Boards

The selection of a precise therapy on the basis of a patient’s molecular profile requires computer-assisted analysis of enormous molecular, clinical, patient history, and pharmacological data sets that often come from disparate sources. For instance, arriving at an optimal decision may involve searching through tens of thousands of unique variants in ClinVar,27 more than 5 million somatic variants in the Catalogue of Somatic Mutations in Cancer,28 more than 25 million PubMed articles, more than 0.9 billion submissions to dbSNP,29 190 FDA–approved drugs with pharmacogenomic labeling and more than 300,000 globally registered clinical trials.30 Scientific publications remain a central source of information on the actionability of biomarkers. With advancement in tumor molecular profiling and cancer drug development, scientific evidence is witnessing a huge surge. For doctors commonly with time constraints, presenting just the therapeutically relevant information would ease the time pressure and expedite the biomarker-matched treatment selection process. To create a library of intelligently filtered oncologist-useful information such as drug, disease, biomarker alteration, biomarker-drug relations, manual curation from high-quality journals is often required on a day-to-day basis. In the pancreatic VTB example, biomarker-drug associations were scored on the basis of strength of evidence (preclinical or clinical) and grouped into implication levels as follows: 0 = pertinent negative, 1 = uncertain, 2 = evidence that could modify options, and 3 = biomarker alterations that are highly actionable.

After selecting biomarker-matched treatment, it is equally important for an oncologist to determine the accessibility of a recommended treatment. One recent study found that 19 of 95 patients (20%) were unable to enroll in a recommended study because of trial eligibility restrictions or inconvenient travel distances.13 Poor structuring of eligibility requirements at ClinicalTrials.gov is therefore an issue. Although each trial has inclusion and exclusion criteria, the actual enrollment information is spread throughout the sections in a listed clinical trial. For example, a trial might
include “solid tumor” in its title but specify a particular tumor type in its inclusion criteria or specify a particular subtype in its exclusion criteria. Treatment setting (i.e., what line of treatment a patient eligible is for), although most often included in the inclusion and exclusion criteria, is sometimes included in the official title. A biomarker-based search might list biomarker-specific clinical trials, but it is important to know whether an alteration in a specific biomarker excludes or includes a patient. For example, EGFR exon19 deletion might be an inclusion requirement, but EGFR T790M might be present as an exclusion criterion. Therefore, to know the accurate eligibility criteria, manual population of clinical trial eligibility requirements is performed. This is continuously updated with any new information gathered either via our medical review panel or elsewhere (e.g., trial arm closure). There are many consortia and government-based efforts such as ClinGen31-34 that have disease-specific task forces that standardize such evidence from somatic testing laboratories.

**Usability and Cognitive Systems Analysis of Virtual Tumor Boards**

The success of software applications, especially those built for clinicians and scientists, is dependent on understanding the complex cognitive processes of the intended users and their unique workflows. With this knowledge one can develop a user interface that is more intuitive, is easy to use, and, most important, meets the functional needs of the user. Human factors engineering and usability analysis facilitate users’ reasoning and support their decision making to arrive at the best treatment decisions for their patients and can be applied to VTBs.

Usability testing on VTB prototypes ensures that products meet the design objectives.35,36 Some common techniques for usability testing are think-aloud protocols and eye tracking. To better understand the connection between the design of the prototypes and user experience, one can track how a user visually processes the information on the interface. This attention to usability will help ensure that target oncology users will find their actions intuitive and easy to interpret.

**PATIENT PRIVACY AND INFORMATION SECURITY**

With molecular testing, one possible risk is breach of confidentiality through the release of identifying information. Because it may deeply affect an individual’s sense of self, the privacy of patients with genetic disorders needs to be fiercely protected. All clinicians and researchers involved in this field are very sensitive to this and routinely enforce this in their daily practices. To minimize this risk, DNA samples and medical data are typically encoded and linked to a registry participant identification number. The link between contact information and personal identifying information is maintained at a single location, accessible only to honest brokers and principal investigators of the study or VTB. Any breach of confidentiality should be immediately reported to the institutional review board of record and the sponsor (e.g., National Institutes of Health).

Potential risks associated with clinical whole-exome sequencing are anticipated to be similar to risks associated with other forms of genetic testing, including anxiety and stress at learning the results, disrupted family relationships, possible disruption in social relationships, changes in reproductive choices, stigmatization, and potential loss of employability or insurability (although this potential is now lessened because of the Genetic Information Nondiscrimination Act). In addition, because whole-exome sequencing also produces incidental genetic information, there may be unforeseeable risks systems, and processes must be in place for appropriate return of results. Study enrollment and disclosure of genetic test results are typically performed in the context of genetic counseling by board-certified geneticists and genetic counselors to minimize these potential risks. During the informed consent process, individuals must be provided with alternatives for clinical genetic testing so that they can make informed decisions about whether to participate in the precision medicine research program. Participants may also change their minds and decline to learn their results prior to the test result disclosure session.

Precision medicine informatics platforms must therefore adhere to all federal regulations for handling sensitive data including the Health Insurance Portability and Accountability Act and the Federal Information Security Management Act. National Institutes of Health–funded programs are required to adopt and implement the policies, procedures, controls, and standards of the U.S. Department of Health and Human Services Information Security Program by aligning with data access policies and eRA Commons authentication framework. Large consortia sharing genomic data from thousands of participants use a secure virtual private cloud framework that provides the security controls necessary to meet Federal Information Security Management Act compliance requirements. Through this infrastructure, information protection is provided with security controls at the virtual network, server, and storage layer as well as the security controls offered by cloud providers such as Amazon Web Services. Teams must implement identity management, authentication and authorization services, storage security, and logging and event management to effectively secure patient derived precision medicine data sets.

**CONCLUSION**

Taken together, leveraging the rapid advances in precision medicine technologies to deliver the greatest benefits to patients is incredibly promising while at the same time constrained by considerable challenges. Using precision oncology requires innovative comprehensive programs to overcome barriers to implementation and scalable learning systems to keep pace with the huge and growing fund of knowledge and rapidly changing technological advances. Here we present two methods of precision medicine informatics, via clinical decision support software methodologies and a modern version of a classic tumor board. Either method will permit treatment of patients and also facilitate the collection, storage, and sharing of molecular and clinical data. This step is essential, as learning from the past is
the only way to improve the collective care provided to patients in the future. Specific to bioinformatics, sophisticated, cloud-based platforms adhering to strict security standards are being developed to manage and analyze complex omics data. These rapidly evolving systems allow routine clinical care and can also facilitate the use of virtual experts. Developing and strengthening collaborations (private, public, and government; laboratory and clinic) remain key in quickly achieving the promises of precision medicine.

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References


HEMATOLOGIC MALIGNANCIES—LEUKEMIA, MYELODYSPLASTIC SYNDROMES, AND ALLOTRANSPLANT
Acute Myeloid Leukemia: The Good, the Bad, and the Ugly

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OVERVIEW

Acute myeloid leukemia (AML) was initially subdivided according to morphology (the French-American-British system), which proved helpful in pathologic categorization. Subsequently, clinical and genomic factors were found to correlate with response to chemotherapy and with overall survival. These included a history of antecedent hematologic disease, a history of chemotherapy or radiation therapy, the presence of various recurrent cytogenetic abnormalities, and, more recently, the presence of specific point mutations. This article reviews the biology and responses of one AML subgroup with consistent response and good outcomes following chemotherapy (core-binding factor leukemia), and two subgroups with persistently bad, and even ugly, outcomes (secondary AML and TP53-mutated AML).

THE GOOD: CORE BINDING FACTOR ACUTE MYELOID LEUKEMIA—ALL ARE CURED?

There are two kinds of spurs, my friend. Those that come in by the door; those that come in by the window. – Tuco the Ugly in The Good, the Bad and the Ugly

Diagnosis

Core-binding factor (CBF) AML includes AML with t(8;21)(q22;q22) and AML with inv(16)(p13q22) or t(8;21)(p13;q22) chromosomal rearrangements [hereafter referred to as t(8;21) and inv(16)], leading to the RUNX1-RUNX1T1 and CBFB-MYH11 fusion genes, respectively. Both alterations result in the disruption of genes encoding subunits of the CBF complex (RUNX1 and CBFB), a heterodimeric transcription factor complex that regulates hematopoietic differentiation. CBF-AML is among the most common cytogenetic subtypes of AML, accounting for 25% of pediatric cases of AML and 15% of adult de novo AML cases. Their identification is critical in routine practice because the presence of these alterations substantially affects clinical management of AML. Morphologically, patients with t(8;21) frequently present with the French-American-British (FAB) morphologic subtype M2 or AML with maturaƟ on, whereas patients with inv(16) are more often diagnosed with the FAB M4Eo or acute myelomonocytic leukemia with abnormal marrow eosinophils. Importantly, patients with t(8;21) or inv(16) should be considered to have AML regardless the percentage of blasts, according to the World Health Organization (WHO) classification of hematologic neoplasms.

Additional chromosomal aberrations, which are detected by conventional karyotype in approximately 70% and 40% of t(8;21) and inv(16), respectively, are distributed in a non-random fashion, and some of them are extremely rare in non–CBF AML (Fig. 1). Among t(8;21) cases, loss of a sex chromosome is by far the most common event, occurring in near half of patients, followed by del(9q) in 10% to 20% of cases. Both aberrations are nearly absent among inv(16) cases. Although the prognosis conferred by these aberrations has been debated, it is believed that they do not affect the outcome in t(8;21) patients. By contrast, trisomy 22 appears specific to inv(16) and represents the most frequent secondary aberration in this subset, in which it accounts for 10% to 20% of cases. Several reports, including one from the German-Austrian AML study Group (AMLSG), have suggested that trisomy 22 was associated with more favorable outcome.

Experience from murine models has demonstrated that the expression of the RUNX1-RUNX1T1 or CBFB-MYH11 fusion genes alone induces aberrant self-renewal and impairs differentiation but is insufficient to induce leukemia. Consistent with this, preleukemic cells harboring RUNX1-RUNX1T1 or CBFB-MYH11 fusion genes were identified in neonatal Guthrie tests more than 10 years before clinical development of AML, as well as following long-term clinical remission of AML. CBF-AML is therefore considered as a model for the multistep pathogenesis of leukemia, in which AML development requires the acquisition of further lesions, including mutations activating kinase signaling.
Common Kinase Signaling Alterations

Mutations activating kinase signaling, especially in genes encoding transmembrane tyrosine kinase receptors KIT and FLT3, or intracellular small guanosine triphosphatases belonging to the RAS family, are the most frequent secondary events in CBF AML (Fig. 1). Mutations involving this set of genes are found in 30% to 75% of patients depending on sequencing panels, technologies, and depth of coverage.\(^{10,15-20}\) Signaling mutations have been a great field of research in recent years, but data are still conflicting; however, most published reports indicate that KIT mutations confer an adverse prognosis, with a higher incidence of relapse.\(^{9,15,16,20,21}\)

Overall, the discrepancies among studies may reflect differences in treatment, including salvage therapy, selection of the study cohort, or the methods of investigation. The prognostic significance of KIT mutations may depend on allelic burden,\(^{15,22,23}\) as well as other cooperating events.\(^{15}\) Indeed, results from the United Kingdom Medical Research Council suggested a higher relapse rate in patients with a KIT mutant level of 25% or greater,\(^{23}\) whereas the French group found a higher incidence of relapse in t(8;21) patients with a KIT mutant allelic ratio of 35% or more.\(^{15}\) To date, the effect of FLT3 mutations is even more controversial among studies and could depend on the type of mutations,\(^{24}\) whereas RAS mutations have never been correlated with clinical outcome. These uncertainties translate into cautionary recommendations; CBF AML with KIT mutations has been reclassified into intermediate-risk group in the National Comprehensive Cancer Network recommendations but are not mentioned in the European LeukemiaNet 2017 risk stratification.

Distinct Genetic Patterns in t(8;21) and inv(16) AML

Recent reports identified recurring mutations that distinguish t(8;21) and inv(16) AML (Fig. 1).\(^{14,17}\) Indeed, ASXL1 mutations were recently reported in about 11% of t(8;21) cases\(^{25,26}\) as mutations within ASXL2, the paralog of ASXL1, were found in about 23% of t(8;21) cases.\(^{24-25}\) Strikingly, these mutations were totally absent among inv(16) patients. Both genes encode proteins that control gene expression through the regulation and the recruitment of epigenetic regulator complexes and transcription factors to specific genomic loci with histone modifications. In a more comprehensive study, it appeared that mutations in genes encoding chromatin modifiers (ASXL1, ASXL2, EZH2, KDM6A, BCOR, BCORL1) could be found in more than 40% of patients with t(8;21). Likewise, mutations within cohesin members (SMC1A, SMC3, RAD21, STAG2) were found in 18% of t(8;21) patients. Both classes of mutations are absent or extremely rare in inv(1).\(^{14,18,26,27}\) Of note, SMC1A, STAG2, BCOR, BCORL1, and KDM6A are located on chromosome X, and loss of sex chromosomes is common in t(8;21) AML, whereas this is rare in inv(16) AML. Interestingly, recent findings about ASXL2 and cohesin dysregulation have suggested a common pathway in which mutations within these two classes of lesions enhanced global chromatin accessibility at RUNX1- and RUNX1-RUNX1T1–specific binding sites.\(^{28,29}\) In a French cohort, t(8;21) patients with mutations in kinase signaling plus chromatin modifiers or cohesin members had the highest risk for relapse.\(^{25}\) Additionally, mutations in ZBTB7A, encoding a negative regulator of glycolysis, have been described in 10%–23% of t(8;21), whereas they appear to be absent in inv(16).\(^{26,28}\)

Minimal Residual Disease

Both RUNX1-RUNX1T1 and CBFB-MYH11 fusion transcripts are well-established markers for measurable residual disease (MRD) monitoring by real-time quantitative polymerase chain reaction. The best time to assess MRD and the threshold to adopt remain a matter of debate and depend on the treatment used. Higher MRD absolute levels or low MRD log-reduction after one or two courses have been associated with a higher risk for relapse in both CBF subgroups and a shorter survival in inv(16) cases.\(^{16,30}\) Postconsolidation MRD monitoring allows for molecular relapse detection, which usually precedes full hematologic relapse from 3 to 4.9 months depending on CBF subtype.\(^{31,32}\) On the basis of these observations, the European LeukemiaNet MRD Working Party recently recommended that patients with CBF AML should have an initial assessment of MRD after two cycles of chemotherapy, followed by serial measurements every 3 months for at least the first 2 years after the end of treatment to detect molecular relapse.\(^{33}\) A molecular relapse is defined by an increase in MRD of 1 log_{10} or greater between two positive samples in a patient with previously undetectable MRD. Of note, stable levels of bone marrow MRD may be detectable for years after initial diagnosis without progression or evidence of hematologic relapse.\(^{31,32}\)

Therapy

A 7 + 3 induction with 3 days of anthracycline and 7 days of continuous infusion of cytarabine remains the standard of care in AML, including CBF AML. The complete remission rate reported in young adults with CBF AML is usually 80%
to 90% or more, with 5-year overall survival (OS) of more than 60%; this is far higher than in other AML subtypes.6,7,17 This high remission rate is also reached in elderly patients after intensive chemotherapy induction, but 5-year OS estimates are lower (30%).34 The benefit of more intensive induction approaches remains unclear. Few trials have been designed in the CBF AML population, and only subgroup analyses with inadequate power are available to assess the benefit of certain therapeutic strategies. The benefit in terms of OS and event-free survival of higher doses of daunorubicin (90 mg/m² × 3 vs. 45 mg/m² × 3) was suggested in the HOVON/AMLSG/SAKK and ECOG-ACRIN studies.35,36 This observation was, however, not confirmed by the Korean Cooperative Study Group A for Hematology group.37 There is no evidence that the early use of intermediate or high cytarabine (I/HDAC) may improve patient outcome.38,39 The French ALFA group randomly assigned patients to receive a standard 7 + 3 regimen or a reinforced induction strategy, with no difference in term of complete response (CR) rate.17 Interestingly, the reinforced strategy was associated with significantly

FIGURE 1. (A) Genetic Landscape and (B) Alterations Frequencies in Core-Binding Factor Acute Myeloid Leukemia (Adult CBF-2006 and Pediatric ELAM-02 Trials)
lower postremission MRD levels that did not translate into differences in terms of cumulative incidence of relapse or OS.17

Since the observation by the CALGB of the benefit of HDAC consolidation in CBF AML, the use of this regimen has widely spread through many cooperative groups.40 The question of the accurate cytarabine dose in consolidation has been raised in many randomized trials. The Japanese Acute Leukemia Study Group reported on the benefit in term of disease-free survival from HDAC consolidation (2,000 mg/m² × 10, five cycles) when compared with conventional-dose (200 mg/m² × 5, four cycles) cytarabine.41 However, no benefit in term of OS was observed. Different studies comparing different dosing and regimens of cytarabine but in which patients were receiving at least one course of I/HDAC during induction or consolidation courses did not accurately define the optimal cytarabine consolidation regimen in CBF AML.39 It is thus recommended that optimal consolidation should consider giving two to four courses of at least 1,000–1,500 mg/m² × 6 (D1, 3, 5, or D1–3) cytarabine.3 In elderly patients, a retrospective study suggested a benefit of intermediate- to high-dose cytarabine in t(8;21) but not in inv(16) patients.44

Allogeneic hematopoietic stem cell transplant (HSCT) is usually not recommended for patients with CBF AML in first CR.3 In the absence of randomized studies, this recommendation is based on numerous donor versus no-donor or allograft versus chemotherapy studies.6,41-43 Recent identification of new risk factors based on MRD assessment or mutation profiling may challenge this position in some subgroups of high-risk patients. Increased cumulative incidence of relapse observed in the context of high postinduction MRD levels or with KIT mutations, especially with high allelic ratios, raises the issue of HSCT indication in this context,16,22,30 especially in younger patients and/or in patients with few comorbidities.44,45

The recent approval of gemtuzumab ozogamicin (GO) as a first-line treatment of AML is an important step forward in the treatment of CBF AML. Several randomized studies have investigated the place of frontline GO in induction and consolidation with different dosage and infusion schedules.46-50 All these studies have reported a benefit of GO in term of relapse-free survival for patients with favorable-risk AML. An individual patient data meta-analysis of these studies confirmed that the benefit of GO is mostly observed in the favorable cytogenetic subgroup, with a difference in OS of 20.7% at 6 years (75.5% vs. 54.8% in GO vs. non-GO group; p = .0006).51 A remaining issue is the benefit/risk ratio of the combination of GO with standard chemotherapy: Few of these patients will be eligible for HSCT, and treatment-related mortality is low after standard induction and I/HDAC consolidation, especially in young patients.

Because of the specific spectrum of mutations associated with CBF AML, the combination of chemotherapy with targeted therapies is a focus of interest. The French Dasact study failed to demonstrate any benefit of dasatinib given as single-agent treatment during maintenance therapy in high-risk CBF AML, defined by a high MRD level after induction.52 In a phase Ib/IIa study, the AMLSG group combined dasatinib with induction, HDAC consolidations, and maintenance in patients with CBF AML, whatever the mutation profile.53 On the basis of favorable safety and an improved OS compared with historical controls, a phase III study is ongoing. According to the same rationale, the Alliance conducted a similar phase II combination, with promising early results.54 The more recent comprehension of oncogenesis and mutational landscape in this disease opens the door to multiple combined approaches, including hypomethylating agents, histone deacetylase, and tyrosine kinase inhibitors.

If CBF AMLs are diseases with “good” prognosis, patients not cured after frontline therapy should not be considered “bad or ugly.” Second complete remission rates in patients exposed to intensive salvage were reported in up to 70% to 80% of patients, and 5-year OS was 30% to 50%. After relapse, second CR rates and OS are usually better in patients with inv(16) than in those with t(8;21).6,7,54,55 The use of GO in salvage regimen improved patient outcome in a retrospective study.56 An indication for HSCT in second CR is widely admitted, although conflicting data have been published on its benefit, especially in t(8;21) cases.55,56

Conclusions
Given the similarities in prognostic and molecular features (involvement of the CBF complex, coexistence of signaling mutations), t(8;21) and inv(16) are usually grouped and reported together in clinical studies. However, recent discoveries of recurring mutations that occur exclusively or almost exclusively in t(8;21) further support the existence of a specific pathway in this group of diseases. Understanding the functional basis for the existence of such lesions will be critical to promote our knowledge of CBF AML and to refine their prognostic relevance.

SECONDARY AML (THE BAD)

Every gun makes its own tune. – Blondie in The Good, the Bad and the Ugly

Diagnosis
Secondary AML is a composite designation that classically alludes to AML that has arisen in the context of a prior myeloid malignancy, newly diagnosed AML that presents with marked dysplasia, or AML that emerges after prior cytotoxic chemotherapy or radiation for an unrelated malignancy. The 1997 WHO classification of hematopoietic and lymphoid neoplasms separated secondary AML from de novo AML, creating a classification system for AML that included the following subcategories: AML with recurrent genetic abnormalities, AML with multilineage dysplasia, therapy-related AML (t-AML) and myelodysplastic syndromes (MDS), and AML not otherwise categorized.57 The 2016 WHO criteria defines AML with myelodysplastic-related changes as a diagnosis of AML that followed a 6-month history of MDS or MDS/myeloproliferative neoplasm (MPN) or presented with
at least 50% dysplasia in two or more myeloid lineages, with the notable exception of cases harboring an NPM1 mutation or biallelic CEBPA mutations. Specific MDS-related cytogenetic abnormalities can represent MDS in the absence of clear morphologic evidence of dysplasia. Recent work suggests that mutations involving spliceosome machinery and chromatin remodeling may be able to identify patients with secondary-like AML with inferior responses to cytotoxic therapy and outcome, although this has not been incorporated into the WHO diagnostic criteria.

Although t-AML is often included under the umbrella of secondary AML, this designation is based on extrinsic exposure as opposed to pathologic findings. Classically, t-AML has been separated according to inciting agent; type 1 t-AML follows treatment with an alkylating agent or ionizing radiation and type 2 follows treatment with a topoisomerase II inhibitor.

Epidemiology
Secondary AML occurs more commonly in the elderly population than does de novo AML, which has a flat incidence throughout life. Large population-based studies suggest that secondary AML makes up about 25% of all AML cases, with 18% to 20% evolving from a previous myeloid disease and 6% to 8% being therapy related (Fig. 2). All myeloid malignancies are associated with an increased risk for AML, although that risk varies widely according to the specific myeloid disease. For many diseases, prognostic risk scores have been developed to better identify patients at increased risk for leukemic transformation. In MDS, patients with excess blasts (MDS-EB1/2) are estimated to have a 25% and 35% risk for AML at 1 and 2 years, with lower-risk MDS having 5% and 10% transformation risk over similar time intervals. MPNs have varying risks of leukemic transformation; primary myelofibrosis is more prone to transformation (estimated at 6%–21% at 5 years and approximately 20% at 10 years) than is both polycythemia vera (2% at 10 years and 8% at 20 years) and essential thrombocytosis (approximately 2% risk at 15 years). MDS/MPN overlap syndromes can carry a substantial risk for leukemic transformation, with a 20% risk attributed to chronic myelomonocytic leukemia and a 40% risk with atypical CML. Bone marrow failure syndromes, such as aplastic anemia and Fanconi anemia, can display leukemic transformation as well. Secondary AML is independently associated with poor rates of response to intensive chemotherapy and inferior OS compared with de novo AML; however, these outcomes are strongly influenced by patient age, karyotype, and preceding myeloid disease. Survival is estimated to be only 6 to 12 months despite treatment with intensive chemotherapy, a prognosis that is disturbingly consistent across age groups, although the disease is heavily enriched in the elderly population. AML arising from MPN or another non-MDS myeloid malignancy appears to be associated with comparatively worse outcomes than AML arising from MDS.

Biology
Secondary AML is biologically distinct from de novo AML, with several key differentiating features: It is associated with multilineage dysplasia, it often harbors a complex karyotype with frequent loss of genetic material, it evolves within a context of clonal hematopoiesis, and it develops as a result of progressive genetic damage. In contrast, de novo disease is believed to result from an inciting genomic event that leads to expansion of the leukemic clone, AML arising from MDS or MPN typically evolves in a stepwise fashion with multiple hits accumulating over time. Thus, patients with secondary AML tend to exhibit more mutated genes than do those with de novo AML. Mutations in SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR, and STAG2 are highly specific for secondary AML, although additional mutations in signaling pathways (i.e., FLT3, RAS,
CBL, PTPN11), transcription factors (i.e., RUNX1, WT1), epigenetic regulators (i.e., IDH1/2, TET2), and TP53 have been implicated in the leukemogenic process. Ultimately, the founding clone is outcompeted by an advantaged subclone, although evidence of the original clone invariably persists. This leads to oligoclonal disease with evolved clones that are differentially responsive to therapy.\textsuperscript{52,85-90} Disease progression has also been attributed to DNA hypermethylation, which leads to silencing of tumor suppressor genes, growth regulatory genes, and adhesion molecules.\textsuperscript{91,92} Decreased response rates in secondary AML have been linked to a multidrug-resistant phenotype. MDR1 encodes P-glycoprotein, a protein that mediates drug efflux and is enriched in patients with AML evolving from MDS. P-glycoprotein participates in active efflux of daunorubicin; is associated with decreased intracellular daunorubicin levels, resistance to induction chemotherapy, and increased relapse rates; and is independently associated with inferior OS.\textsuperscript{93-99} Chemoresistance is also conferred by upregulation of the antiapoptotic proteins, Bcl-2 and Bcl-X\textsubscript{L}, which undergo splice isoform switching in secondary AML.\textsuperscript{100-105} A comparison of the ratio of proapoptotic (Bax/Bad) to antiapoptotic proteins (Bcl-2/Bcl-X) between low-risk and high-risk MDS showed that disease progression was associated with significantly reduced ratios, due primarily to increased Bcl-2 expression.\textsuperscript{82} Lastly, patients with secondary AML have often received prior therapies that contribute to decreased responsiveness to subsequent therapies. Exposure to hypomethylating agents leads to upregulation of the immune checkpoints PD-1, PD-L1, PD-L2, and CTLA-4, and patients with secondary AML who had prior hypomethylating agent exposure have shown decreased response rates to induction therapy and inferior OS.\textsuperscript{84,106}

Therapy-related AML has been classically separated into two types according to prior exposure. Type 1 t-AML typically occurs 4 to 7 years after treatment, with two thirds of patients experiencing a preceding MDS phase and the other third presenting with AML with MDS-related changes. Deletions of the long arm of chromosome 5 [del(5q)], the long arm of chromosome 7 [del (7q)], or loss of chromosome 7 (monosomy 7) are common, as are TP53 mutations. Numerous candidate genes on chromosome 5 and 7 have been implicated in the pathogenesis of t-AML, suggesting the presence of a contiguous gene syndrome that leads to a resultant state of haploinsufficiency.\textsuperscript{107} In type 2 t-AML, the latency period is typically shorter, with patients often presenting with AML 2 to 3 years after treatment, without a preceding MDS phase and with balanced chromosomal translocations involving 11q23 (MLL) or 21q22 (RUNX1).\textsuperscript{108} Topoisomerase II inhibitors have also been implicated in more rare forms of t-AML, including CBF t-AML and therapy-related acute promyelocytic leukemia. The former displays rearrangements at CBF genes RUNX1 at 21q22 and CBFB 16q22 and typically respond favorably to intensive chemotherapy regimens. The latter displays a balanced translocation between the PML and RARA genes, t(15;17), and responds well to all-trans retinoic acid–based therapies.\textsuperscript{109} Host susceptibility plays an important role in t-AML; many patients with t-AML are found to have germline mutations in cancer susceptibility genes.\textsuperscript{110-112} Interindividual variability in drug metabolism has also been implicated.\textsuperscript{108,113} Similar to AML arising from prior myeloid malignancy, clonal hematopoiesis can play an important role, especially in type 1 t-AML cases in which cytotoxic therapy places a selective pressure on a minor drug-resistant preleukemic clone, allowing for clonal expansion. To that end, reports have shown that mutant TP53 mutant clones can be found in hematopoietic cells years before cytotoxic therapy and are ultimately followed by TP53 mutant therapy-related MDS/AML.\textsuperscript{114,115} Accordingly, evidence of clonal hematopoiesis before cytotoxic therapy is much more common in patients who ultimately develop therapy-related myeloid neoplasms.\textsuperscript{116,117} More recently, the role of the bone marrow microenvironment has been implicated as the role of inflammation in myeloid malignancies has been uncovered.\textsuperscript{118-120}

**Traditional Therapies**

Historically, AML arising from MDS or with evidence of marked dysplasia was treated in a fashion similar to that used for de novo AML, with anthracycline-based chemotherapy regimens and strong consideration of allogeneic hematopoietic cell transplant (AHCT) as the only therapy with curative potential. With these approaches, retrospective reviews have repeatedly shown that outcomes in secondary AML are inferior to those seen with de novo AML, with lower rates of complete remission and frequent relapses.\textsuperscript{121-124} Early efforts to improve treatment responses largely involved intensifying induction chemotherapy regimens, although these efforts were largely unsuccessful.\textsuperscript{125-128} Several randomized clinical trials assessed the addition of P-glycoprotein inhibitors to standard induction regimens, with two trials using cyclosporine-A showing modest clinical benefit.\textsuperscript{129,130}

Additional efforts to improve upon traditional chemotherapy-based approaches relied on increasing the sensitivity of leukemic blasts to chemotherapy by altering cell cycle kinetics. Myeloid growth factors were incorporated on the basis of the rationale that they could enhance the effect of S-phase-dependent cytotoxic agents, such as cytarabine.\textsuperscript{131,134} A Polish study showed impressive results in patients with relapsed/refractory AML treated with cladribine, mitoxantrone, and cytarabine given concurrently with granulocyte colony-stimulating factor CLAG-M),\textsuperscript{135} whereas a retrospective study in patients with AML evolving from MDS after azanucleoside failure and showed improved response rates and survival with CLAG-M compared with standard induction.\textsuperscript{136}

Secondary AML has long been viewed as a high-risk disease that requires AHCT for the achievement of durable remission. No prospective studies have compared AHCT to nontransplant treatments, and retrospective studies have yielded conflicting results.\textsuperscript{128,137-139} Through use of propensity score matching, outcomes with AHCT were similar between de novo AML and secondary AML, although it is important to note that numerous factors thought to predict poor response after AHCT are enriched in the secondary AML population.\textsuperscript{139}
Azanucleosides
Azacitidine (Aza) and decitabine are nucleoside analogs that incorporate into DNA and inhibit DNA methyltransferase. They have been extensively studied in MDS and secondary AML, given the importance of DNA methylation in progression from MDS to AML.91,92 The AZA-001 trial led to the approval of Aza for the treatment of MDS after showing a survival benefit compared with conventional care. This study included patients with 21% to 30% blasts who would now be classified as having AML with myelodysplastic-related changes.140 The AZA-AML-001 study subsequently enrolled patients age 65 or older with newly diagnosed AML and more than 30% bone marrow blasts and randomly assigned them to Aza or conventional care. Aza-treated patients showed a trend toward improved OS, although this gained statistical significance only after patients receiving conventional care were censored at time of crossover. A post hoc central review of patients’ bone marrow samples from this trial identified that more than 50% of study participants met criteria for AML with MDS-related changes, and a subgroup analysis demonstrated that these patients exhibited a survival advantage with Aza.141 Although Aza has limited benefit in the chronic phase of MPNs, it is commonly used in the blast phase and can lead to clinical responses.142,143

Decitabine was directly compared with conventional care in a phase III study that enrolled patients age 65 or older with newly diagnosed AML with poor or intermediate-risk cytogenetics. Secondary AML was reported in 35% of patients. Although primary analysis did not reveal a significant improvement in OS (7.7 months vs. 5.0 months; p = .108), response rates were significantly improved and a subsequent, unplanned analysis after prolonged follow-up demonstrated improved OS, with a nominal p value of .03 showing statistical significance.144 Retrospective data have also suggested benefit in MPNs with accelerated or blast phase and high-risk myelofibrosis.145

Guadecitabine, a next-generation hypomethylating agent that is resistant to deamination and has a longer half-life than Aza and decitabine, has been tested in AML in early-phase trials that are enriched with patients who have secondary AML. Promising results in a recently published phase II trial have led to an ongoing phase III trial comparing guadecitabine to conventional care in previously untreated AML.146

Sapacitabine (CYC682) is an oral nucleoside analog that induces single-strand breaks and leads to double-strand DNA breaks and/or G2 cell cycle arrest. Although early-phase studies showed promising activity, two phase III studies have failed to meet their primary endpoints.147,148

CPX-351
The importance of ratiometric dosing was demonstrated preclinically in a study that analyzed several combinations of chemotherapy, including cytarabine and daunorubicin. This led to the creation of CPX-351, a liposomal encapsulation of cytarabine and daunorubicin at a fixed ratio of 5:1, which was shown to be the optimal ratio to achieve synergistic activity in mouse studies.149 The unique delivery system leads to improved drug delivery and prolonged exposure.150,151 A randomized phase II study compared CPX-351 to investigator’s choice of salvage therapy in relapsed AML and demonstrated improved responses and a potential survival advantage in patients with poor-risk AML, a group that was enriched in this study population.152 This led to the development of a randomized phase III clinical trial comparing CPX-351 to standard 7 + 3 induction chemotherapy in patients with newly diagnosed, high-risk AML age 60 to 75. “High-risk” was defined as prior cytotoxic treatment, antecedent MDS or chronic myelomonocytic leukemia, or AML with MDS-related cytogenetic abnormalities. In this trial, CPX-351 treatment resulted in significantly improved OS (9.56 vs. 5.95 months; p = .005), event-free survival (p = .021), and complete remission plus complete remission with incomplete marrow recovery (47.7% vs. 33.3%; p = .016). A landmark analysis performed in patients from either group who underwent AHCT demonstrated improved OS in those treated with CPX-351, with a hazard ratio of 0.46 (p = .0046). The side effect profile was similar between treatment groups; the notable difference was prolonged count recovery in the CPX-351 group.153 This led to the U.S. Food and Drug Administration (FDA) approval of CPX-351 for the treatment of newly diagnosed t-AML or AML with MDS-related changes. CPX-351 has now become the standard of care for patients with secondary AML who are fit to receive intensive chemotherapy.

Novel Therapeutics
A host of novel agents are being actively investigated in secondary AML, often addressing new targets that convey treatment resistance or contribute to disease progression. Some agents of particular interest are summarized in Table 1.

Conclusions
Secondary AML is a subgroup of AML highlighted by treatment resistance and poor outcomes. Various biologic features contribute to this phenotype; however, our increased understanding has led to the development of novel therapeutic agents that hold promise in improving outcomes in our patients. The FDA approval of CPX-351 for the treatment of newly diagnosed t-AML and AML with MDS-related changes represents an important step forward in the battle to improve care for our patients. In looking toward the future, further therapeutic advances related to personalized molecular phenotyping are emerging, along with a better understanding of risk-mitigation strategies to help prevent t-AML in vulnerable populations.

TP53-MUTATED AML (THE UGLY)
Put your drawers on and take your gun off. – Blondie in The Good, the Bad and the Ugly

TP53-mutated AML is a subset of AML with especially poor response to chemotherapy and consistently dismal outcomes.154
<table>
<thead>
<tr>
<th>Drug Target</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Trial</th>
<th>Phase</th>
<th>Single-Agent vs. Combination</th>
<th>Indications</th>
<th>Relevance to Secondary AML</th>
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<td>Bcl-2 inhibition</td>
<td>Venetoclax (ABT-199)</td>
<td>BH3 mimetic</td>
<td>NCT03069352</td>
<td>III</td>
<td>Combination (low-dose cytarabine)</td>
<td>Treatment-naive AML</td>
<td>Phase II included 47% with antecedent hematologic malignancy</td>
<td>Phase 2: ORR 64%</td>
<td>Recruiting</td>
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<tr>
<td></td>
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<td></td>
<td>NCT02993523</td>
<td>III</td>
<td>Combination (azacitidine)</td>
<td>Treatment-naive AML</td>
<td>Phase II included 25% with sAML</td>
<td>Phase II: ORR 67%</td>
<td>Recruiting</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>NCT03404193</td>
<td>II</td>
<td>Combination (decitabine)</td>
<td>R/R high-risk MDS/AML, treatment-naive AML in elderly patients, sAML</td>
<td></td>
<td>Recruiting</td>
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<tr>
<td>IDH2 inhibitor</td>
<td>Enasidenib (AG-221)</td>
<td>Mutant-specific IDH2 inhibition</td>
<td>NCT03383575</td>
<td>II</td>
<td>Combination (aza)cidine)</td>
<td>HMA-naive MDS, including patients with blasts 20%-30%</td>
<td>Inclusion criteria include AML-MLD with 20%-30% blasts; IDH1/2 mutations seen in 10% of sAML cases</td>
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<td></td>
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<td></td>
<td>NCT02577406</td>
<td>III</td>
<td>Single-agent</td>
<td>R/R de novo or secondary AML in elderly</td>
<td>Phase Ib/II portion included ≥25% with secondary AML</td>
<td>Phase II: ORR 40%; median OS 9.3 mo</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td>NCT03013998</td>
<td>II</td>
<td>Stepwise</td>
<td>Treatment-naive AML</td>
<td>Previously untreated patients; IDH1/2 mutations seen in 10% of sAML cases</td>
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<td>Recruiting</td>
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<td></td>
<td>NCT02632708</td>
<td>I</td>
<td>Combination (induction)</td>
<td>Treatment-naive AML</td>
<td>43% of enrolled patients with sAML</td>
<td>57% ORR in sAML</td>
<td>Recruiting</td>
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<tr>
<td>IDH1 inhibitor</td>
<td>Ivosidenib (AG-120)</td>
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<td>Expanded access</td>
<td>Single-agent</td>
<td>R/R AML</td>
<td>IDH1/2 mutations seen in 10% of sAML cases</td>
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<td>Available</td>
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<td>NCT03173248</td>
<td>III</td>
<td>Combination</td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td>Combination (induction)</td>
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<td>31% of enrolled patients with sAML</td>
<td>44% ORR in sAML</td>
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<table>
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<tr>
<th>Drug Target</th>
<th>Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Trial</th>
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<th>Relevance to Secondary AML</th>
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<td>Immune checkpoints</td>
<td>Nivolumab and ipilimumab</td>
<td>PD-1 and CTLA-4</td>
<td>NCT02397720</td>
<td>II</td>
<td>Combination (azacitidine)</td>
<td>De novo and R/R AML in elderly patients</td>
<td>43% of enrolled patients with sAML with poor-risk cytogenetics</td>
<td>ORR 35%; CR in 21%</td>
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<td>Pembrolizumab</td>
<td>PD-1</td>
<td>NCT02845297</td>
<td>II</td>
<td>Combination (azacitidine)</td>
<td>De novo and R/R AML in elderly patients</td>
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<td>Recruiting</td>
</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
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<td>NCT03065400</td>
<td>II</td>
<td>Single-agent</td>
<td>MPN-AP and MPN-BP</td>
<td>Recruting</td>
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<td></td>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>NCT02775903</td>
<td>II</td>
<td>Combination (azacitidine)</td>
<td>De novo and secondary AML in elderly patients</td>
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<tr>
<td>Spliceosome</td>
<td>H3B-8800</td>
<td>SF3B1 modulator</td>
<td>NCT02841540</td>
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<td>Single-agent</td>
<td>MDS, CMML, AML with splicing mutation</td>
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<td>AML or high-risk MDS</td>
<td>Strong preclinical rationale in post-PMN AML</td>
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<td>INCB057643</td>
<td>BET inhibitor</td>
<td>NCT02711137</td>
<td>I/II</td>
<td>Single-agent/combination</td>
<td>Advanced malignancies</td>
<td>Expansion phase includes combination arm with ruxolitinib</td>
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</tbody>
</table>

Abbreviations: AML, acute myeloid leukemia; ORR, objective response rate; sAML, secondary acute myeloid leukemia; R/R, relapsing/refractory; MDS, myelodysplastic syndrome; HMA, hypomethylating agent; MLD, multilineage dysplasia; OS, overall survival; CR, complete response; MPN-AP, myeloproliferative neoplasm in accelerated phase; MPN-BP, myeloproliferative neoplasm in blast phase; CMML, chronic myelomonocytic leukemia; BET, bromo domain and extra-terminal; MPN, myeloproliferative neoplasm; MF, mycosis fungoides.
Diagnosis

TP53-mutated AML carries mutations in TP53. These mutations are widely distributed across all domains of the gene, although there is a bias toward the DNA-binding domain. All forms of mutations have been observed, including deletions, insertions, and nonsense mutations, but the majority of variants are missense (70%–80%). There are a series of “hot-spot” positions, including P72R, R175H, Y220C, R248Q, and R273C, and these patterns largely overlap between AML-associated mutations and TP53 variants observed in solid tumors. This bias toward “hot-spot” positions reflects a shift in the mutational spectrum of AML-associated TP53 mutations, and 32% of TP53 mutations are C>G variants, whereas only 7% of global AML mutations are C>G variants. Mutations in different domains may represent different functional effects (gain of function vs. loss of function). These are generally lumped together in AML studies because of small numbers, and the differential biology of these variants has been incompletely explored in AML. Of note, deletion of the remaining wild-type TP53 allele, or alternative loss of heterozygosity mechanisms, is common, which leads to a null state or affects the dominant-negative or gain-of-function mutations.

Incidence

TP53 mutations occur in nearly 50% of cancer but occur in only 10% to 15% of AML cases. Likewise, Li-Fraumeni syndrome is associated with germline TP53 mutations, but AML is an unusual malignancy among patients with Li-Fraumeni (approximately 5% of associated malignancies). Variants in TP53 are conspicuously absent from pediatric AML. There is a prevalence of TP53 mutations among patients with M6-erythroleukemias (25%–36%), and TP53 mutations have been associated with the progression of AML from polycythemia vera and essential thrombocytopenia.

Historical Outcomes

Across a wide range of studies, responses to cytotoxic induction chemotherapy among patients with TP53-mutated AML tend to be poor (28%–42%) and OS short (median survivals of 5–9 months). In multivariate analysis, TP53 mutations have been associated with inferior responses and OS across a range of studies. Four studies have evaluated the independent impact of complex karyotypes and TP53 mutations on OS of patients treated with cytotoxic chemotherapy. These studies found combinatory effects but also observed that the adverse risk for complex karyotypes is driven predominantly by the presence of TP53 mutations and that TP53 outcomes may be worse with concurrent TP53 and complex karyotypes.

Biology

TP53 mutations in AML are associated with older age, lower blast counts (both in the bone marrow and in the peripheral blood), adverse risk karyotypes, and exposure to antecedent chemotherapy. TP53 mutations tend to have high variant allele frequencies and are nearly universally stable at relapse, all consistent with early events during clonal evolution.

Analysis of co-occurring mutations has suggested that TP53-mutant AML clusters as a unique subgroup; however, TP53-mutated AML is not associated with a unique transcriptional signature by standard RNA sequencing. TP53 mutations co-occur with a paucity of other common AML-associated single-nucleotide variants (e.g., DNMT3A, NPM1, FLT3, IDH1, IDH2, TET2); rather, TP53-mutated AML is associated with recurrent co-occurring karyotypic structural alterations, especially abnormalities involving chromosomes 5, 7, and 17 and with events involving chromothripsis. Interestingly, although genomic instability has been attributed to TP53 dysfunction, only specific types of augmented mutagenesis are noted in TP53-mutated AML; TP53-mutations co-occur with increased numbers of large cytogenetic events, chromothripsis, and marker chromosomes, but not with an increase in single-nucleotide variants.

To better define patterns of nucleotide variants and mutations in TP53, we performed a meta-analysis of published TP53-mutated AML cases that included sequence evaluation of at least 16 additional genes, and we identified 248 cases (Fig. 3A). Consistent with individual studies, TP53-mutated cases are associated with a paucity of additional nucleotide variants; 50% of cases lacked co-occurring variants in any of these additional 16 genes, whereas 75% of cases in The Cancer Genome Atlas presented with variants in at least one of these genes. Reduced frequency of co-occurring mutations was particularly prominent among a few AML-defining genes, including NPM1 and FLT3. Frequencies were also reduced in IDH1, IDH2, DNMT3A, WT1, and RUNX1, and a trend toward an increase in the frequency of JAK2 variants was observed, consistent with TP53 associating with transformation from myeloproliferative diseases.

Mutations may coexist within founding clones or subclones or may exist in alternative clones, which are unrelated to the malignant clone. We observed a case with a TP53 mutation that responded to decitabine, in which a DNMT3A mutation was observed in an alternative clone that expanded during remission and was subsequently displaced at relapse (Fig. 3B). To determine whether co-occurring nucleotide variants commonly co-occur within founding clones with TP53, we examined 65 available cases with concurrent mutations in DNMT3A, TET2, FLT3, or N/KRAS (the most commonly comutated genes), where the variant allele frequency of both the TP53 mutation and the concurrent mutation were publically available (Fig. 3C). Most variants colocalized along the median, suggesting that they co-occur within founding clones. A subset of variants could be observed with high TP53 variant allele frequency and low variant allele frequency in the concurrent gene (suggesting the concurrent variant is in a subclone or an alternative clone), and a subset of variants were observed with
low TP53 variant allele frequency and high variant allele frequency in the concurrent gene (suggesting the TP53 variant is in a subclone or in an alternative clone). These data are consistent with the finding that TP53 variants typically contribute to early founding clone evolution, and the occasional participation of TP53 variants in subclonal expansion or in AML transformation.

TP53 point mutations may result in conformation changes that disrupt the TP53 protein or direct disruption of the DNA-binding interface. Both effects lead to loss of DNA binding. Dominant negative effects may occur through hetero-oligomerization with the wild-type TP53 protein. Novel functions of many of the point mutations have been accessed by overexpressing the missense allele in TP53 null tumor cells and observing acquired phenotypes; specifically, an increase in growth independence, tumor progression, metastasis, and drug resistance has been associated with missense TP53 variants, suggesting gain-of-function activities.

Overexpression of wild-type TP53 in the context of tumor cells with null versus mutant TP53 tumor cells lead to incomplete restoration of the mutant expression signatures, again suggesting novel functions of the mutant proteins that could not be restored by re-expression of the wild-type allele. The extent of the mutant expression signature varied, depending on the mutation; R172H had the greatest effect (one of the most common conformational mutations), whereas expression of wild-type TP53 could abrogate the effects of R270H to a greater degree (a DNA contact mutation).

Wild-type TP53 protein has a short half-life. Many of the missense mutations lead to protein stabilization and thus to high concentrations of mutant TP53 protein, and this heightened protein level may facilitate some dominant-negative or gain-of-function effects. Mechanisms of high mutant TP53 expression have not been clearly elucidated in AML but may include decreased ubiquitination and disruption of normal MDM2 negative feedback mechanisms on TP53 expression.

The mechanisms of leukemogenesis in TP53-mutated AML remain unclear. Within the subset of erythroleukemia, direct cross-talk between Gata1 and Tp53 has been described, suggesting potential lineage-restricted leukemic activity.
TP53 mutations are observed in preleukemic states such as clonal hematopoiesis of indeterminate prognosis and thus appear capable of directly providing a clonal, premalignant advantage.\textsuperscript{198-200} The frequent co-occurrence of chromosomal abnormalities in chromosomes 5 and 7 suggest that specific additional pathways must be modified to transition from clonal hematopoiesis of indeterminate prognosis to AML. Likewise, TP53 mutations may be observed in hematopoietic stem/progenitor clones that exist before chemotherapy, which are subsequently selected for by the evolutionary bottleneck imposed by chemotherapy.\textsuperscript{201}

Activation of TP53 has been implicated as an essential step in chemotherapy-induced apoptosis.\textsuperscript{202,203} Therefore, it is not surprising that TP53 mutations are enriched in treatment-related myeloid neoplasms and that TP53-mutated AML responds poorly to chemotherapy that induces DNA damage and cellular stress and cell death via TP53-activating mechanisms.

**Treatment Options**

The first question is, should patients with TP53-mutated AML avoid treatment? Indeed, compared with other forms of AML, TP53-mutated AML has dismal outcomes and typically represents the molecular subgroup with the worst outcomes in prognostic studies. However, despite these results, patients with TP53-mutated AML who did not receive chemotherapy fared even worse,\textsuperscript{172} so the presence of TP53 alone should not be an absolute barrier to therapy.

Logically, the choice of therapy should be directed toward options that do not require activation of TP53 to achieve responses. In this way, we come back to Blondie's gritty recommendation, “Put your drawers on and take your gun off.” TP53-mutated AML may best be approached with something other than the usual cytotoxic hand cannons applied to standard AML.

Decitabine, at low doses, does not cause direct cytotoxicity but is incorporated into DNA, where it acts to alter epigenetic signatures.\textsuperscript{90,204} Several studies have found that the presence of adverse-risk karyotypes did not affect the response rates or OS of patients treated with decitabine.\textsuperscript{205-209} Ten-day cycles of decitabine induced responses in 21 of 21 patients with TP53 mutations, and these patients had equivalent outcomes compared with TP53 wild-type patients.\textsuperscript{90} More recent studies using 5-day schedules of decitabine noted 62% and 66% response rates in TP53-mutated AML or MDS cases, respectively.\textsuperscript{156,210} and cell-line analysis further suggests a potential sensitivity of TP53-mutated cells to hypomethylating agents.\textsuperscript{211} Despite recent enthusiasm for decitabine, decitabine as a single-agent does not induce deep or durable remissions, and additional consolidation therapy is necessary.\textsuperscript{90,212}

Alternative approaches will be required to target this ultra-high-risk group of patients with AML. Novel therapies in development aim to restore or stabilize the expression of a remaining wild-type allele, destabilize the mutant protein, or activate TP53-independent cell death.\textsuperscript{157-159,197} Targeting potential synthetic lethality pathways has also been explored.\textsuperscript{157} Such targets include the G2/M checkpoint (because TP53 mutant cells tend to have lost G1 arrest activity) and growth signaling pathways that TP53 null cancer cells rely on (especially easily targeted kinases); however, it is unclear whether these synthetic lethality approaches will be universally applicable or will be cell type specific. Many of these studies have been performed in epithelial cancer cell lines, and it remains to be seen whether they can easily be translated to AML.

Recently, small molecules have been developed that specifically destabilize individual TP53 point mutants, with efforts focused on R175H, R248Q, R273H, and Y220C.\textsuperscript{157} These are exciting, targeted therapies but may be challenging to assess in AML clinical trials because of limited numbers of patients with specific mutations. Alternative compounds, such as PRIMA-1, appear able to facilitate refolding of mutant TP53 into wild-type configurations, and these may be more clinically tractable simply as a result of patient numbers.\textsuperscript{213} Regardless, such target-directed therapies hold much promise, and clinical results will be eagerly anticipated, although limited patient numbers in AML may be challenging for clinical trial completion.

One particularly interesting class of TP53-targeting therapies are the statins, which lead to preferential degradation of mutant TP53 in cancer cell lines\textsuperscript{192,214} and to ex vivo toxicity of primary AML cells.\textsuperscript{215,216} Follow-up studies found that perturbation of the mevalonate synthesis pathways by statin induced a ubiquitin ligase that preferentially targeted mutant TP53 for degradation.\textsuperscript{214} In vitro statin concentrations required for mutant TP53 degradation are typically in the 1 to 10 μM range, whereas typical human serum concentrations are 1 to 50 nM.\textsuperscript{217} Therefore, short-term high-dose statin may need to be considered.

**Conclusions**

TP53 mutations inform a unique subset of AML associated with recurrent karyotypic variants, an absence of recurrent single nucleotide variants, and dismal responses to cytotoxic chemotherapy. Decitabine has emerged as an alternative approach, with a TP53-independent mechanism of action. Unconventional strategies and targeted therapeutics will be required to overcome the adverse risk associated with TP53 mutations.

**SUMMARY**

A growing molecular and biologic understanding of AML has allowed us to view the disease in an increasingly nuanced way. Historically, identifying the good, the bad, and the ugly forms of the disease helped select patients likely to require more aggressive therapeutic interventions after standard induction chemotherapy. The FDA approval of GO and CPX-351, coupled with the impressive results of decitabine in TP53 mutated AML, has signaled the emergence of a tailored initial approach. Returning to our cinematic analogy, it was Blondie who stated, “Every gun makes its own tune.” Often as deadly as a firearm, AML is similarly unique, but with newly approved medications and promising novel
agents under investigation, there is reason for optimism in our ability to develop the optimal counterattack.

ACKNOWLEDGMENT

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Incorporating Immunotherapy Into the Treatment Strategies of B-Cell Adult Acute Lymphoblastic Leukemia: The Role of Blinatumomab and Inotuzumab Ozogamicin

Hagop Kantarjian, MD, and Elias Jabbour, MD

OVERVIEW

Monoclonal antibodies and bispecific antibody constructs hold considerable promise in improving the outcomes of patients with acute lymphoblastic leukemia (ALL). Antibody-drug conjugates such as inotuzumab ozogamicin and the bispecific T-cell engager blinatumomab represent novel antibody constructs that have shown substantial clinical activity in ALL. Although most studies have focused on the use of these agents in the salvage setting, incorporation of these antibodies into the frontline regimens is imperative to improve long-term survival for patients with ALL and to increase the cure rates of adult ALL to the levels achieved in the pediatric population.

Recent years have witnessed major advances in the development of novel therapies that target specific subsets of adult acute lymphoblastic leukemia (ALL).1 Monoclonal antibodies, bispecific antibody constructs, and chimeric antigen receptor (CAR) T-cell therapies developed in the past 5 to 7 years have revolutionized the treatment of ALL and resulted in U.S. Food and Drug Administration approvals of blinatumomab (2014), inotuzumab (2017), and tisagenleucel (2017) as ALL salvage strategies.2-5 These agents bind to selective targets on leukemic cells and work through a number of mechanisms, including antibody-dependent and complement-dependent and cellular cytotoxicity and direct induction of apoptosis. If a target is known to internalize upon binding, potent drugs or toxins can be conjugated to the antibody portion, producing an additional mechanism for leukemic cell targeted elimination.2 These agents bind to selective targets on leukemic cells and work through a number of mechanisms, including antibody-dependent and complement-dependent and cellular cytotoxicity and direct induction of apoptosis. If a target is known to internalize upon binding, potent drugs or toxins can be conjugated to the antibody portion, producing an additional mechanism for leukemic cell targeted elimination.2

Minimal Residual Disease

PREAMBLE

Although adults with ALL achieve high rates of complete remission (CR) of 90% with frontline modern chemotherapy regimens, approximately 40% to 50% relapse. The overall response rates after relapse are low, ranging from 25% to 50%. Cytotoxic chemotherapy results in modest CR rates of 30% to 40% in first salvage and 10% to 20% in later salvages. Few patients can be bridged to allogeneic stem cell transplantation (allo-SCT), with 5% to 10% in some studies but as high as 30% to 40% in German trials.6,7 Bridging to allo-SCT offers a chance of long-term remissions and cures (< 20%–30%). Immunotherapy, in the form of monoclonal antibodies and bispecific antibody constructs, targeting CD19 and CD22, and CAR T-cell therapies have allowed better management of relapsed-refractory B-cell ALL.

ANTI-CD19 BISPECIFIC T-CELL ENGAGER: BLINATUMOMAB

CD19 is nearly universally expressed on the cell surface of both precursor and mature B-ALL leukemic blasts and is therefore an ideal target for antibody-directed therapy. Blinatumomab, the first bispecific T-cell–engaging antibody construct, redirects host CD3-positive T cells to cell surface antigen-expressing (CD19) ALL cells (Table 1).8

Minimal Residual Disease

Postinduction MRD positivity is an independent prognostic marker of chemotherapy-refractory disease in both adult and pediatric ALL. Blinatumomab was first assessed in patients with positive MRD and subsequently studied in patients with relapsed-refractory ALL. Gökbuget et al8 used single-agent blinatumomab in 116 patients with ALL in first or later CR
CR. Blinatumomab was given at 15 μg/m²/day by continuous intravenous infusion for 4 consecutive weeks on a 6-week cycle was associated with a rate of CR plus CR with incomplete hematologic recovery of 43%. The median response duration was 9 months; the median survival time was 6 months.10 A phase III randomized trial (the TOWER study) compared blinatumomab with an investigator’s choice chemotherapy in patients with relapsed/refractory Ph-negative ALL.4 More than 400 patients were randomly selected (2:1) to receive either blinatumomab (271 patients) or standard-of-care (SOC) chemotherapy (134 patients). The overall response rate was 45% with blinatumomab and 30% with SOC (p = .007). Molecular remission rates among responders, defined as less than 10⁻⁴ blasts in the first 12 weeks, were 75% and 48%, respectively. Blinatumomab prolonged survival, which was the primary study endpoint. The median survival was 7.7 months (range, 5.6–9.6 months) with blinatumomab and 4.0 months (range, 2.9–5.3 months) with SOC chemotherapy, respectively (hazard ratio [HR], 0.71; p = .012). Better results were obtained when blinatumomab was used in salvage 1: in this setting, median survival was 11.1 with blinatumomab and 5.5 months with SOC.

Studies assessing blinatumomab in the frontline treatment of adults ALL are ongoing.

**Ph-Positive Acute Lymphoblastic Leukemia**

Blinatumomab was evaluated in the phase II ALCANTARA trial in patients with relapsed/refractory Ph-positive ALL.11 Blinatumomab was given at the standard dose for up to five cycles in 45 patients. After the first two cycles, 36% of patients achieved CR or partial hematologic response. With a median follow-up duration of 9 months, the median relapse-free survival was 6.7 months, and the median survival was 7.1 months. Among the 16 responders, the MRD negativity rate was 88%. Forty-four percent of patients received allo-SCT.

Blinatumomab was evaluated in combination with ponatinib, a potent BCR-ABL1 tyrosine kinase inhibitor, in 20 patients with relapsed/refractory Ph-positive ALL and chronic myeloid leukemia in lymphoid blast phase.12 The combination was safe and resulted in an objective response rate of 65%. The median survival was 14 months. Studies combining ponatinib and blinatumomab are ongoing in older patients with newly diagnosed Ph-positive ALL and in relapsed/refractory Ph-positive ALL.

The toxicity profile of blinatumomab is acceptable, consisting of fever, chills, and hypogammaglobulinemia. Tremor, headache, other mental status changes (e.g., confusion), and occasional seizures (2%) have been reported. Fever, chills, and other constitutional symptoms are due to a cytokine release syndrome that occurs shortly after the start of therapy. This is reduced with the use of steroids (e.g., dexamethasone 8 mg every 8 hours for 2 or 3 days). Serious adverse events are uncommon and include encephalopathy and rarely seizures. Corticosteroids before the first dose and prior to dose escalation ameliorate some toxicities.

**ANTI-CD22 ANTIBODY-DRUG CONJUGATE: INOTUZUMAB OZOGAMICIN**

CD22 is expressed in 95% of precursor B-ALL and universally in Burkitt leukemia. Inotuzumab ozogamicin is an immunoconjugate comprised of an anti-CD22 antibody linked to calicheamicin, a potent cytotoxic compound (Table 2).13 In

### TABLE 1. Blinatumomab Activity in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ph-Positive</th>
<th>Ph-Negative</th>
<th>Positive MRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>45</td>
<td>189</td>
<td>271</td>
</tr>
<tr>
<td>CR/CRh/CRi, %</td>
<td>36</td>
<td>43</td>
<td>45</td>
</tr>
<tr>
<td>MRD* negativity, %</td>
<td>88</td>
<td>82</td>
<td>76</td>
</tr>
<tr>
<td>OS, median, mo</td>
<td>7.1</td>
<td>6.1</td>
<td>7.7</td>
</tr>
</tbody>
</table>

*MRD negativity defined by a level less than 0.01%.

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; CR, complete response; CRh, complete response with incomplete hematologic recovery; CRi, complete response with incomplete blood count recovery; NA, not applicable; OS, overall survival.

but with MRD positivity. Most patients had three or more courses of chemotherapy, and at least 35% were in second CR. Blinatumomab was given at 15 μg/m²/day by continuous infusion for 28 days every 6 weeks for four cycles. Approximately 78% of patients achieved MRD negativity after one cycle and 80% after four cycles.3 With a median follow-up duration of 29 months, the median survival was 36 months, and the median relapse-free survival was 19 months. The median survival for patients who achieved MRD-negative status was 40 months, compared with 12 months for those who remained MRD positive.9 Notably, allo-SCT did not confer a survival benefit for the small number of patients (14 patients) who achieved MRD negativity in first remission. These results provide evidence that a strategy of MRD-directed therapy using monoclonal antibodies and bispecific-antibody constructs is useful in improving outcome in ALL.

### Relapsed-Refractory Disease

In the confirmatory phase II study of 189 heavily pretreated patients with relapsed or refractory Philadelphia chromosome (Ph)–negative ALL, blinatumomab given as a continuous intravenous infusion for 4 consecutive weeks on a 6-week cycle was associated with a rate of CR plus CR with partial hematologic recovery of 43%. The median response duration was 9 months; the median survival time was 6 months.10 A phase III randomized trial (the TOWER study) compared blinatumomab with an investigator’s choice chemotherapy in patients with relapsed/refractory Ph-negative ALL.4 More than 400 patients were randomly selected (2:1) to receive either blinatumomab (271 patients) or standard-of-care (SOC) chemotherapy (134 patients). The overall response rate was 45% with blinatumomab and 30% with SOC (p = .007). Molecular remission rates among responders, defined as less than 10⁻⁴ blasts in the first 12 weeks, were 75% and 48%, respectively. Blinatumomab prolonged survival, which was the primary study endpoint. The median survival was 7.7 months (range, 5.6–9.6 months) with blinatumomab and 4.0 months (range, 2.9–5.3 months) with SOC chemotherapy, respectively (hazard ratio [HR], 0.71; p = .012). Better results were obtained when blinatumomab was used in salvage 1: in this setting, median survival was 11.1 with blinatumomab and 5.5 months with SOC.

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TABLE 2. Inotuzumab Ozogamicin Activity in Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single Dose Phase II</th>
<th>Weekly Dose Phase II</th>
<th>Weekly Dose Multicenter Phase II</th>
<th>INO-VATE Phase III</th>
<th>INO + Mini-Hyper-CVD R/R</th>
<th>INO + Mini-Hyper-CVD Frontline Elderly</th>
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</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>49</td>
<td>41</td>
<td>35</td>
<td>109</td>
<td>70</td>
<td>52</td>
</tr>
<tr>
<td>INO dose/schedule</td>
<td>1.8 mg/m² D1 q 3–4 weeks</td>
<td>0.8 mg/m² D1</td>
<td>0.8 mg/m² D1</td>
<td>0.8 mg/m² D1</td>
<td>1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4</td>
<td>1.3–1.8 mg/m² in cycle 1 followed by 1.0–1.3 mg/m² for cycles 2–4</td>
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</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>ORR, %</th>
<th>57</th>
<th>59</th>
<th>68</th>
<th>88</th>
<th>77</th>
<th>97</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %</td>
<td>18</td>
<td>20</td>
<td>31</td>
<td>36</td>
<td>59</td>
<td>80</td>
</tr>
<tr>
<td>MRD negativity, %</td>
<td>68</td>
<td>71</td>
<td>84</td>
<td>78</td>
<td>81</td>
<td>96</td>
</tr>
<tr>
<td>Median survival, mo</td>
<td>5</td>
<td>7.3</td>
<td>7.4</td>
<td>7.7</td>
<td>11</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

Abbreviations: ALL, acute lymphoblastic leukemia; INO, inotuzumab ozogamicin; R/R, refractory/refractory; D, day; ORR, overall response rate; CR, complete response; MRD, minimal residual disease.

A single-institution phase II study in patients with relapsed/refractory ALL, inotuzumab was administered at a starting dose of 1.3 to 1.8 mg/m² intravenously every 3 to 4 weeks.14 Forty-nine patients were treated, 73% of whom received inotuzumab for second salvage or later. The objective response rate was 57%, and the median survival was 5.1 months. Nearly half of the patients treated with inotuzumab were able to proceed to allo-SCT (22 patients), including four patients who received second allo-SCT. Common adverse effects included fever and hypotension following the infusion. Notable serious toxicities included veno-occlusive disease after allo-SCT (23%). This was observed mainly in patients who received double alkylators as part of their pretransplantation conditioning. Older age was also a risk factor, with older patients experiencing more veno-occlusive disease after allo-SCT compared with younger patients.

To minimize toxicities without compromising efficacy and on the basis of pharmacokinetic and pharmacodynamic data, inotuzumab was administered on a weekly basis at 0.8 mg/m² intravenously on day 1, followed by 0.5 mg/m² intravenously on days 8 and 15, every 3 to 4 weeks in 40 patients with relapsed/refractory ALL.15 The study yielded a similar objective response rate as inotuzumab given every 3 to 4 weeks (59% vs. 57%) with a median survival of 9.5 months. Weekly administration of inotuzumab resulted in fewer adverse events, including lower rates of veno-occlusive disease. In a separate multicenter phase II trial in heavily pretreated patients with relapsed/refractory ALL, inotuzumab therapy resulted in a remission rate of 66%, with 78% of patients who achieved CR becoming MRD negative. The median survival was 7.4 months.16

In a randomized phase III trial comparing inotuzumab with a physician’s choice of chemotherapy in patients with relapsed/refractory ALL in salvage 1 and 2, the objective response rates were 88% (CR 81%) with inotuzumab and 32% (CR 29%) with SOC chemotherapy (p < .0001). Among responders, the MRD-negativity rates were 78% and 28% (p < .0001), respectively. The median progression-free survival was 5.0 with inotuzumab versus 1.8 months with SOC (p < .001). The median survival was 7.7 versus 6.7 months (HR 0.77; p = .02); the 2-year survival rate was 23% versus 10%.3 The median progression-free survival was 5.0 months with inotuzumab and 1.8 months with SOC (HR 0.45; p < .001).

Combination Therapy in Acute Lymphoblastic Leukemia Salvage

Inotuzumab was evaluated in the salvage setting in combination with a dose-reduced “mini-hyper-CVD” regimen including low doses of hyperfractionated cyclophosphamide (50% dose reduction), vincristine, no anthracyclines, and dexamethasone alternating with low doses of methotrexate (75% dose reduction) and high-dose cytarabine (83% dose reduction).17 Fifty-nine patients with relapsed/refractory ALL were treated. The objective response rate was 78% (CR 59%), with 82% of responders achieving MRD-negative status. Results are updated in the 70 patients treated so far (Table 2). The 2-year progression-free and survival rates were 60% and 32%, respectively. Among patients treated in salvage 1, the 2-year survival rate was 50%. The survival of patients treated with mini-hyper-CVD plus inotuzumab were superior to a historical cohort of patients with relapsed-refractory ALL treated with inotuzumab monotherapy (median survival, 11 months vs. 6 months; p = .03).17 Studies exploring lower dose schedules of inotuzumab (0.9 mg/m² per cycle) in relapsed-refractory ALL and in patients with MRD-positive disease are ongoing.

Elderly Patients With Acute Lymphoblastic Leukemia

The incidence of ALL increases after the age 50. In this patient population, intensive chemotherapy results in a CR rate of 80% but a high rate of toxicities.18,19 One-third of patients achieving CR die of myelosuppression-associated complications during consolidation maintenance. The long-term cure rate among such patients is only 15% to 20%.18,19 The German Multicenter Study Group for Adult ALL reported a CR rate of 76%, an early death rate of 14%, a mortality of 6% in CR, and a 5-year survival rate of 23% in 268 elderly patients treated with less-intensive induction and consolidation regimen.20 Among 727 elderly patients (> age 65) diagnosed between 2007 and 2012 and treated under Medicare, the median survival was 10 months.21 In the National Cancer
Institute’s Surveillance, Epidemiology, and End Results database (1980–2011), among 1,675 older patients with ALL (age ≥ 60), the median survival time was 4 months, and the 3-year survival rate was 12.8%. The goal with modern regimens is to maintain efficacy but reduce toxicity.

In a phase II study, 52 patients (median age, 69; range, 60–79 years) with newly diagnosed Ph-negative ALL were treated with mini-hyper-CVD and inotuzumab. The objective response rate was 97% (CR rate 80%). All patients in CR also achieved MRD negativity. The 2-year CR duration and survival rates were 81% and 64%, respectively. The 2-year survival rates were higher with mini-hyper-CVD plus inotuzumab than with historical hyper-CVAD with or without rituximab (64% vs. 38%, respectively). A validation of these preliminary findings in a randomized phase III trial is planned.

**Ph-Positive Acute Lymphoblastic Leukemia**

Inotuzumab was evaluated in combination with bosutinib in 16 patients with relapsed-refractory Ph-positive ALL (14 patients) and chronic myeloid leukemia in lymphoid blast phase (2 patients). The combination was safe and resulted in an objective response rate of 81% (CR 50%). The complete cytogenetic response and complete molecular response rates were 69% and 55%, respectively. The median event-free and overall survival were 8.8 and 10.7 months, respectively. Among the 13 responders, six received allo-SCT; five are alive at the last follow-up.

**OTHER AGENTS IN DEVELOPMENT**

Other antibody-drug conjugates targeting CD19 and CD22 are in development. Among them, ADCT-402 is composed of a humanized monoclonal antibody directed against human CD19, conjugated to SG3199, a pyrrolobenzodiazepine dimer cytotoxin. The potential for ADCT-402 in treating B-cell malignancies was tested in mice injected subcutaneously or intravenously with cells from human-derived B-cell leukemia and lymphoma cell lines. Complete responses were observed in mice after receiving a single low dose of ADCT-402. The efficacy of ADCT-402 in these models is due to the targeted delivery of the cytotoxin. In a phase I study in 29 patients with relapsed-refractory ALL, single-agent ADCT-402 15 to 150 μg/kg weekly × 3 every month was well tolerated, with no dose-limiting toxicities. Four patients responded at the higher dose levels (3 CR, 1 CR with incomplete blood count recovery), with two MRD-negative CRs. Dose escalation and expansion are underway.

**CAR T-CELL THERAPIES**

CAR T-cells are an exciting recent development in cancer treatment. CAR T cells directed at CD19 and CD22 are an effective approach for patients with aggressive B-cell lymphomas and pediatric ALL. In the initial study, 59 children with relapsed/refractory ALL were treated with CAR T cells. The CR rate was 93%. The estimated 1-year event-free and survival rates were 55% and 79%, respectively. Cytokine release syndrome occurred in 88% of the patients, all of whom recovered. In a confirmatory phase I/II, 25-center global study, 75 patients age 3 to 23 (median, age 11) were treated. The overall remission rate within 3 months was 68% (82% among patients who were evaluable for efficacy). All responders achieved negative MRD status. The event-free survival and overall survival rates were 50% and 73% at 12 months, respectively.

In the ZUMA-3 study, 33 patients with relapsed/refractory ALL were treated. The overall response rate was 71% (CR 67% and CR with incomplete blood count recovery 4%). Overall, the rate of grade 3 or higher cytokine release syndrome was 28%; the rate of any grade 3 or higher neurologic events was 52%.

Recently an adult study of CD19 CAR T cells was reported. Eighty-three patients were enrolled, 78 underwent pheresis, and 53 were treated. CR was observed in 44 of the 53 patients treated (CR rate 83%; CR in 44 of 78 who underwent pheresis [56%]). For the 53 patients treated, the median event-free survival was 6.1 months, and median survival was 12.9 months. The 2-year event-free survival and survival rates were about 15% and less than 30%, respectively. Patients with low disease burden (defined as marrow blasts < 5%) had longer event-free survival and survival durations, as well as lower incidences of cytokine release syndrome neurotoxic events.

To circumvent CD19 escape as a cause of relapse after CD19–CAR T-cell therapy, CD22-targeted CAR T-cell therapy has recently been developed. Of the 15 children and adults with relapsed/refractory B-ALL, most of whom were previously treated with CD-19-directed immunotherapy, 11 (73%) achieved CR after treatment with at least 1 × 10^6/kg body weight of CD22-targeted CAR T cells.

Current CAR T-cell therapies use autologous lymphocytes, which can be scarce and difficult to expand. New platforms provide an “off-the-shelf” approach, in which cells are derived from healthy volunteer donors. Preliminary results of the CALM study (UCART19 in Advanced Lymphoid Malignancies) using this therapy in a phase I dose escalation trial were recently reported. Among six adults, four achieved CR with incomplete blood count recovery with MRD negativity at day 28. Off-the-shelf products targeting CD22 and allogeneic cord blood–derived natural killer cells are being developed.

**CONCLUSION**

Therapies targeting specific transcripts or leukemic cell surface antigens are major therapeutic breakthroughs. In the relapsed/refractory setting, the use of immunotherapy results in high rates of MRD negativity, which translated into long-term survival in some responders, particularly when given in salvage 1. For example, when inotuzumab was given in combination with low-intensity chemotherapy, a median survival duration beyond 2 years was obtained. Given the encouraging results achieved with monoclonal antibodies, bispecific antibody constructs, and CAR T cells, the therapeutic tools necessary to improve outcomes of patients with adult ALL may now be available. These treatment modalities are not competitive but rather complementary, and they could be administered sequentially to produce the deepest remissions possible. With these therapeutic options, the question is how they are best incorporated into ALL treatment. The rational combination
of monoclonal antibodies, bispecific antibody constructs, and CAR T cells may reduce the need for long-term intensive chemotherapy and may obviate the need for allo-SCT in many patients. These novel combinations may translate into improved long-term outcomes and may result in cure rates in adult ALL that approach those seen in the pediatric population.

References


HEMATOLOGIC MALIGNANCIES—LYMPHOMA AND CHRONIC LYMPHOCYTIC LEUKEMIA
The advent of novel small molecule therapy for the treatment of CLL has dramatically changed the therapeutic landscape. Two B-cell receptor inhibitors, ibrutinib and idelalisib, are now available. Ibrutinib, a Bruton’s tyrosine kinase inhibitor, has approval by the U.S. Food and Drug Administration for the initial treatment of CLL and for relapsed disease. Idelalisib, a phosphoinositide 3-kinase delta inhibitor, is approved when combined with rituximab for the treatment of relapsed CLL. In addition, venetoclax, a BCL2 inhibitor, was approved for the treatment of relapsed CLL in patients with 17p deletion. However, a recent presentation of data from the Murano trial1 (at the 2017 Meeting of the American Society of Hematology), will likely lead to a broader label for this agent in the near future.

The excellent efficacies of these novel agents raise questions about what the future treatment landscape will look like. This paper addresses several topics in CLL relevant to the use of small molecules. The initial section discusses whether there is still a role for chemoimmunotherapy in the treatment of CLL. The second section discusses the challenge of treating CLL in older patients. Although novel agents generally are better tolerated than chemotherapy regimens, they are not without their own particular adverse effects, some of which can be problematic in older patients. In addition, there is the practical issue of the generalized availability of these drugs given the expense involved with their use. Finally, the topic of optimal sequencing of small molecules, including outcomes after switching agents either because of intolerance or resistance, is addressed. These discussions should be helpful for the general management of CLL in the age of oral agents.

IS THERE STILL A ROLE FOR CHEMOIMMUNOTHERAPY IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA?

Role of Chemoimmunotherapy in Treatment-Naive Chronic Lymphocytic Leukemia

In the 1980s and 1990s, the activity of the chemotherapy agents, such as chlorambucil, cyclophosphamide, and fludarabine, was noted in patients with CLL.2 With the introduction of rituximab, chemoimmunotherapy (CIT) regimens, such as FCR (fludarabine, cyclophosphamide, rituximab) and BR (bendamustine, rituximab), were established.3,4 In a phase II trial, the FCR regimen led to an overall response rate (ORR) of 95% with a complete remission (CR) rate of 72%.5 The median progression-free survival PFS was 6.4 years. The value of added rituximab was confirmed by the German CLL Study Group (GCLLSG) CLL8 trial, in which 817 treatment-naive, physically fit patients were randomly assigned to FCR or to fludarabine and cyclophosphamide (FC); the FCR regimen led to improved PFS and overall survival (OS).6 The BR regimen is used often in patients with CLL.7 In the GCLLSG CLL10 trial, 561 treatment-naive, physically fit patients [without del(17p)] were randomly assigned to FCR or to BR.8 The primary endpoint was PFS, which was longer with FCR (median PFS, 57.6 months for the FCR arm vs. 42.3 months for the BR arm; hazard ratio [HR], 1.593; p < .0001).9 There was no difference in OS. Patients in the FCR group were more likely to receive less than the planned six cycles, and they had more myelosuppression and infectious complications. Approximately 35% patients of the patients enrolled in this trial were older than age 65; in that age group,
the PFS for the BR versus FCR group was not different, and BR was less toxic. The CLL10 trial established FCR as the treatment of choice for younger, fit patients with CLL. For patients older than age 65 who are deemed appropriate for CIT, FCR, or BR could be considered. It is important to note that, for patients in whom CIT is considered appropriate but who have moderate renal dysfunction (i.e., glomerular filtration rate [GFR] of 30 to 70 mL/min/1.73 m²), FCR can lead to serious toxicities; for these patients, BR is preferred.

In an effort to identify patients who derive the most long-term benefit from first-line FCR, a research group at MD Anderson Cancer Center reported that patients who have mutated IGHV have a 10-year PFS of approximately 55% compared with approximately 10% for the IGHV-unmutated group. Notably, a plateau was seen on the PFS curve for IGHV-mutated group after 10 years. Other groups have reported similar findings, albeit with a shorter follow-up time. Theses data suggest that, for patients with mutated IGHV, FCR remains an attractive option given long-term disease remission in the majority of the patients; many of these patients had no evidence of disease in the blood by polymerase chain reaction (i.e., negative for minimal residual disease [MRD]), so the possibility of cure has been raised. It is important to mention that up to 5% of patients may develop therapy-related myelodysplastic syndrome/acute myeloid leukemia after FCR. Patients with unmutated IGHV continue to experience disease relapse after CIT. Hence, CIT may not be the optimal approach for treatment in these patients, and treatment with novel targeted therapies should be considered. Limited clinical data with targeted therapies in young, fit patients with CLL [who do not have del(17p)] are available.

Ibrutinib, a Bruton’s tyrosine kinase inhibitor, is currently approved for patients with CLL. Ibrutinib was initially investigated in a phase I/II clinical trial in 101 patients with relapsed/refractory CLL and 31 patients with treatment-naive CLL. In the treatment-naive cohort, after a median follow-up time of 62 months, an ORR of 87% with a CR rate of 29% was noted. The 5-year PFS was an impressive 92%. In a phase III trial (RESONATE-2 trial), 269 patients age 65 or older with treatment-naive CLL were randomly assigned to receive ibrutinib or chlorambucil. The median PFS was significantly longer for the ibrutinib arm (median, not reached for ibrutinib vs. 18.9 months for chlorambucil; HR 0.16; p < .001). The 2-year PFS was 89% for the ibrutinib arm and was 34% for the chlorambucil arm. The OS was significantly superior for the ibrutinib arm even after crossover was allowed for those who experienced progression with chlorambucil (p = .001). This trial led to the expanded label for ibrutinib as initial therapy of CLL. Currently, a randomized clinical trial is comparing ibrutinib/obinutuzumab with chlorambucil/obinutuzumab (PCYC-1130); enrollment has completed, but the results are pending.

Patients with del(17p) are resistant to CIT. Results with targeted therapies, such as ibrutinib and venetoclax, are much superior to those achieved with CIT regimens. CIT should not be used for patients with del(17p).

### Role of CIT in Relapsed/Refractory Chronic Lymphocytic Leukemia

Historically, CIT had been the standard of care for patients with relapsed/refractory CLL. This rapidly changed a few years ago with the introduction of targeted therapies. In the initial phase I/II trial with ibrutinib, 101 patients with relapsed/refractory CLL were enrolled. After a median follow-up time of 49 months, an ORR of 89% with a 10% CR rate was noted. The median PFS for the relapsed/refractory cohort was 52 months. Notably, this group of patients was heavily pretreated with a median of four prior therapies. In comparison, the median PFS with FCR in less heavily pretreated patients with relapsed/refractory CLL has ranged from 21 to 31 months. Similarly, the median PFS with BR in patients with relapsed/refractory CLL (median of two prior therapies) was 15 months. Thus, ibrutinib is superior to CIT in relapsed/refractory CLL. The BCL2 inhibitor venetoclax currently is approved for patients with relapsed/refractory CLL and del(17p). At the recent American Society of Hematology annual meeting, the combination of venetoclax and rituximab (VR) was compared with BR in relapsed/refractory CLL (MURANO trial). A total of 389 patients were enrolled (194 in VR; 195 in BR). The median number of prior therapies for both arms was one. After a median follow-up time of 23.8 months, the PFS was much longer with VR (HR 0.19; p < .0001; median, not reached vs. 18.1 months). The benefit of VR was noted across all patient subgroups. The 2-year PFS was 82.8% for the VR group. VR also led to improved OS (HR 0.48; p = .018). This trial clearly establishes the superiority of targeted therapies compared with conventional chemotherapy in relapsed/refractory CLL. In our opinion, the role for CIT in

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**PRACTICAL APPLICATIONS**

- **Novel agents are currently indicated in both the frontline (ibrutinib) and relapsed/refractory settings (ibrutinib, idelalisib/rituximab, venetoclax).**
- **Although ibrutinib is indicated for all patients in the frontline setting, comparative data on ibrutinib versus chemoimmunotherapy and sequencing after ibrutinib discontinuation are limited; in addition, a subset of fit patients with mutated IGHV experience prolonged remissions and may be cured with FCR.**
- **In older patients (not candidates for FCR or BR), ibrutinib produces significantly higher ORR and longer PFS and OS than those seen with chlorambucil; nevertheless, financial exigencies may prohibit initial therapy with ibrutinib in some patients.**
- **In the relapsed setting, ibrutinib, idelalisib/rituximab, and venetoclax all can be used; however, current data about sequencing these agents are limited to one prospective study and retrospective real-world evidence studies.**
- **Continued enrollment of patients with CLL into clinical trials with relevant controls and observational studies is important to resolve ongoing sequencing questions.**
relapsed/refractory CLL is very limited and likely restricted to patients whose disease has failed to respond to all available targeted therapies or those whose tumors may need rapid debulking.

Combination of CIT and Targeted Therapies
There have been efforts to improve upon CIT with incorporation of targeted therapies. The MD Anderson Cancer Center group reported preliminary results of a clinical trial with the combination of ibrutinib, FC, and obinutuzumab (GA101) for young, fit patients with mutated IGHV and without del(17p). Notably, only three cycles of FC chemotherapy were administered. Patients continued ibrutinib and obinutuzumab for up to a total of 12 cycles. An MRD negativity rate in bone marrow of 87% was reported after three cycles; it was 93% at 6 months. The CR/CRi rate was 44% after three cycles, which increased to 78% after cycle 6. All patients with negative MRD discontinued ibrutinib at 1 year and had no MRD recurrence during a median follow-up of 5.5 months after discontinuation. Researchers from the Dana-Farber Cancer Institute reported results with the combination of ibrutinib with six cycles of FCR in young, fit patients with CLL. This trial included patients with both mutated and unmutated IGHV and included patients with del(17p). A total of 63% patients achieved CR/CRi, and 83% were MRD negative in bone marrow. These data from the ibrutinib/FC/obinutuzumab and ibrutinib/FC/rituximab trials, although obtained with a small number of patients and short follow-up, appear favorable compared with FCR results; the bone marrow MRD negativity rates were especially impressive.

In relapsed/refractory CLL, in the HELIOS trial, patients were randomly assigned to receive BR plus ibrutinib versus BR plus placebo. The BR/ibrutinib arm resulted in a longer PFS and OS. Unfortunately, neither of these trials included a nonchemotherapy arm, and the contribution of bendamustine to the efficacy is unclear.

CIT SUMMARY
The role of CIT has greatly diminished in the era of targeted therapies. First-line CIT with FCR is considered for young, fit patients with mutated IGHV and without del(17p). Notably, only three cycles of FC chemotherapy were administered. Patients continued ibrutinib and obinutuzumab for up to a total of 12 cycles. An MRD negativity rate in bone marrow of 87% was reported after three cycles; it was 93% at 6 months. The CR/CRi (complete response with incomplete hematologic recovery) rate was 44% after three cycles, which increased to 78% after cycle 6. All patients with negative MRD discontinued ibrutinib at 1 year and had no MRD recurrence during a median follow-up of 5.5 months after discontinuation. Researchers from the Dana-Farber Cancer Institute reported results with the combination of ibrutinib with six cycles of FCR in young, fit patients with CLL. This trial included patients with both mutated and unmutated IGHV and included patients with del(17p). A total of 63% patients achieved CR/CRi, and 83% were MRD negative in bone marrow. These data from the ibrutinib/FC/obinutuzumab and ibrutinib/FC/rituximab trials, although obtained with a small number of patients and short follow-up, appear favorable compared with FCR results; the bone marrow MRD negativity rates were especially impressive.

In relapsed/refractory CLL, in the HELIOS trial, patients were randomly assigned to receive BR plus ibrutinib versus BR plus placebo. The BR/ibrutinib arm produced a superior PFS (18-month PFS, 79% in the BR/ibrutinib arm vs. 24% in the BR/placebo arm; HR 0.203; p < .0001). In another phase III trial, patients with relapsed/refractory CLL were randomly assigned to BR plus idelalisib versus BR plus placebo. The BR/idelalisib arm resulted in a longer PFS and OS. Unfortunately, neither of these trials included a nonchemotherapy arm, and the contribution of bendamustine to the efficacy is unclear.

THE CHALLENGE OF CHRONIC LYMPHOCYTIC LEUKEMIA IN THE ELDERLY POPULATION
The median age at diagnosis of CLL is 70 years; approximately 67% of patients are age 65 or older. Historically, there has been a sense of therapeutic nihilism surrounding patients with CLL. This developed from two beliefs: first, that older patients with CLL would die as a result of unrelated causes; second, that there were limited treatment options to greatly affect the natural history of the disease and that were tolerable in the elderly population. In fact, in a large study from the Mayo clinic, all patients—except those age 75 or older with Rai stage 0 disease—had a reduced life expectancy relative to age-matched controls. Other studies have shown that CLL reduces life expectancy, even in patients age 85 or older. Elderly patients have historically been under-represented in clinical trials. However, therapeutic options for older patients have changed dramatically in recent times.

### Table 1. Phase III Trials in Treatment-Naive Chronic Lymphocytic Leukemia

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Control (Chemotherapy)</th>
<th>Experimental (Targeted Therapies)</th>
<th>Current Status</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG-E1912</td>
<td>519</td>
<td>FCR</td>
<td>ibrutinib + rituximab</td>
<td>Enrolled</td>
<td>NCT02048813</td>
</tr>
<tr>
<td>ALLIANCE A041202</td>
<td>523</td>
<td>BR</td>
<td>ibrutinib + rituximab</td>
<td>Enrolled</td>
<td>NCT01886872</td>
</tr>
<tr>
<td>PCYC-1130</td>
<td>212</td>
<td>CLB + G</td>
<td>ibrutinib + G</td>
<td>Enrolled</td>
<td>NCT02264574</td>
</tr>
<tr>
<td>ACE-CL-007</td>
<td>535</td>
<td>CLB + G</td>
<td>acalabrutinib + G</td>
<td>Enrolled</td>
<td>NCT02475681</td>
</tr>
<tr>
<td>BGB-3111-304</td>
<td>467</td>
<td>BR</td>
<td>BGB-3111</td>
<td>Enrolled</td>
<td>NCT03336333</td>
</tr>
<tr>
<td>UNITY-CLL</td>
<td>Approximately 300</td>
<td>CLB + G</td>
<td>TGR1202 + U</td>
<td>Enrolled</td>
<td>NCT02612311</td>
</tr>
<tr>
<td>CLL14</td>
<td>445</td>
<td>CLB + G</td>
<td>venetoclax + G</td>
<td>Enrolled</td>
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</tr>
<tr>
<td>CLL13</td>
<td>920</td>
<td>FCR / BR</td>
<td>venetoclax + G</td>
<td>Enrolling</td>
<td>NCT02950051</td>
</tr>
</tbody>
</table>

Abbreviations: ACAL, acalabrutinib; BR, bendamustine + rituximab; CLB, chlorambucil; CLL, chronic lymphocytic anemia; FCR, fludarabine, cyclophosphamide and rituximab; G, obinutuzumab; IBR, ibrutinib; R, rituximab; U, ublituximab; VEN, venetoclax.
Why Is Age Important and How Do We Assess Fitness?

The age of a patient is linked to life expectancy, which in turn may determine the treatment paradigm: aggressive treatment that is intended to produce deep, durable remission is appropriate for a younger patient with limited comorbidities; in contrast, for an older patient who has severe comorbid conditions that limit life expectancy, palliative treatment intended to avoid excessive treatment-related toxicity may be most appropriate. Additional expected life years according to age and patient sex are listed in Table 2. We may underestimate the life expectancy of many of our older patients.

Chronologic age per se is not the most important determinant of treatment outcome in CLL; however, older patients have an increased incidence of comorbid medical conditions, including physical frailty, which may affect both life expectancy and treatment tolerability. The number of comorbidities independently predicts inferior PFS and survival in both younger and older patients; thus an assessment of fitness, rather than reliance on chronologic age, is essential to inform treatment decisions.

Comprehensive geriatric assessment is recommended by the National Comprehensive Cancer Network and International Society for Geriatric Oncology for patients age 65 or older. Such an assessment should encompass the following domains: functional status, comorbidity, cognition, mental health status, fatigue, social status and support, nutrition, and presence of geriatric syndromes. The purpose of such a review is to select a treatment strategy that is based on functional status, life expectancy, and predicted treatment tolerability. However, such an assessment is time consuming, requires geriatric expertise, and has not been widely adopted in CLL.

Comorbidity assessment tools determine the number and severity of comorbidities; these are widely used to define fitness to describe prognosis and determine clinical trial eligibility. The Cumulative Index Rating Scale (CIRS) is perhaps the most widely used; others include the Charlson comorbidity index and the National Cancer Institute comorbidity index. Eastern Cooperative Oncology Group performance status is simple and rapid to perform in the routine clinic setting, but it provides relatively limited functional assessment in older patients; however, this is often the only assessment of fitness used to determine clinical trial eligibility. CIRS score does not correlate well with performance status.

There are distinct changes in pharmacokinetics in older patients that may increase the risk of adverse effects caused by drug accumulation: Renal function, known to decline with age, is an important determinant of tolerability of fludarabine-based regimens, for example; in addition, hepatic function declines with age. Older patients also are more likely to suffer from polypharmacy; in one study among ambulatory patients with cancer, 84% were receiving more than five medications and 43%, more than 10 medications. Polypharmacy increases the potential for drug-drug interactions. This is important to recognize in patients treated with CLL, because ibrutinib and venetoclax are metabolized predominantly by CYP3A4 enzymes in the liver; adverse effects that result from drug accumulation can be caused by co-prescription of drugs that inhibit CYP3A4 enzymes. Careful review of medication lists for older patients and consideration of organ function are required when treatment decisions are made.

Table 2. Additional Expected Life Years According to Age and Sex

<table>
<thead>
<tr>
<th>Patient Age, Years</th>
<th>Additional Years of Life Expectancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>Men 19.2</td>
</tr>
<tr>
<td></td>
<td>Women 21.7</td>
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<tr>
<td>70</td>
<td>Men 15.4</td>
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<td></td>
<td>Women 10.1</td>
</tr>
<tr>
<td>85</td>
<td>Men 6.2</td>
</tr>
<tr>
<td></td>
<td>Women 7.3</td>
</tr>
</tbody>
</table>

According to U.S. Social Security data.

Prognostic Factors in Older Patients With Chronic Lymphocytic Leukemia

Prognostic factors in patients with CLL have been reviewed elsewhere. The international prognostic index for CLL integrates five independent prognostic factors: TP53 status (no abnormalities vs. del[17p] or TP53 mutation or both), IGHV mutational status (mutated vs. unmutated), serum β2-microglobulin concentration (≤3.5 mg/L vs. >3.5 mg/L), clinical stage (Binet A or Rai 0 vs. Binet B to C or Rai I to IV), and age (≤65 years vs. >65 years) into a weighted prognostic score, which was validated specifically in older patients (i.e., age 70 or older). In CLL, most reports suggest no association between age and higher-risk disease biology, although one report did suggest a higher incidence of TP53 deletion or mutation. Also, reports about the significance of biologic prognostic factors in older patients generally indicate that these factors retain prognostic importance. Data from the Mayo Clinic demonstrated that prognostic markers, such as IGHV mutation status, retained significance at least up to age 75; thereafter, mutation status and fluorescence in situ hybridization appeared to lose prognostic importance; the international prognostic index for CLL remained prognostic for OS in patients older than age 70. As in younger patients, del(17p) or TP53 mutation are important predictive markers; outcomes with CIT are dismal and novel agents, such as ibrutinib and venetoclax, achieve impressive PFS in the relapsed setting. Currently, ibrutinib is approved by the U.S. Food and Drug Administration in the first-line setting, whereas venetoclax is approved for relapsed del(17p) CLL. We believe that IGHV somatic hypermutation status and del(11q) may be used increasingly as predictive markers, because unmutated IGHV and del(11q) predict inferior outcomes with FCR but not with ibrutinib.
Does CIT Still Have a Role in Fit, Older Patients With Chronic Lymphocytic Leukemia?

In fit patients who have favorable prognostic features [i.e., mutated IGHV, lack of del(11q) or del(17p)], FCR may produce long-lasting remissions and, potentially, cure.\(^\text{62-64,67}\) FCR is tolerated by selected older patients; of patients treated with FCR in the GCLLSG CLL8 study, 31% were age 65 or older, and 11% were age 70 or older.\(^\text{17,70}\) All patients had low CIRS scores (≤ 6) and estimated GFR of 70 mL/min/1.73m² or greater. In this study, age was not an independent prognostic factor for either PFS or survival; in addition, hematologic toxicity of grade 3 to 4 severity was only marginally more common (53% vs. 45% for patients age ≥ 65 compared with age < 65), and there was no increased incidence of infection in older patients. Data from the MD Anderson Cancer Center also suggest that PFS is not reduced in patients age 65 or older relative to those younger than age 65 who are treated with FCR.\(^\text{67}\)

Nonetheless, given the high rate of hematologic toxicity, including prolonged neutropenia in 17% to 35% of patients after FCR,\(^\text{62,68}\) the GCLLSG CLL10 study compared BR with FCR as first-line treatment in fit patients with CLL. Notably, although CLL10 showed inferior PFS for BR in the whole-treatment group, there was no PFS difference between the treatment groups in patients age 65 or older, and there was reduced incidence of neutropenia and infection in the BR arm.

An additional concern is a 1.5% to 4.5% incidence of therapy-related myeloid neoplasms after FCR.\(^\text{62,69}\) Second primary cancers are more common after treatment of CLL than in an age-matched population; older age, but not necessarily the specific treatment given, is a risk factor for development of a second primary malignancy after treatment of CLL.\(^\text{17,70}\)

Overall, FCR and BR are reasonable first-line-treatment options for fit, older patients with CLL who lack del(17p) or TP53 mutations. However, FCR is the only therapy demonstrated to achieve very-long-term PFS in patients with favorable genomic features [IGHV mutated, no del(11q), no TP53 deletion or mutation]. Thus, FCR is preferred instead of BR in such favorable-risk patients predicted to be able to tolerate FCR (i.e., fit, age 65 to 70, estimated GFR ≥ 70 mL/min/1.73m²). Phase III studies are ongoing to compare FCR or BR with ibrutinib and venetoclax-based regimens. Older patients are eligible in each study, and each study uses some hematologic, cytotoxicity.\(^\text{71}\) A total of 781 patients were randomly assigned across three arms. Both CD20 monoclonal antibody chemotherapy combinations demonstrated superior PFS relative to that seen with chlorambucil monotherapy (median PFS, 26.7 vs. 16.3 vs. 11.1 months, for G-Clb vs. R-Clb vs. chlorambucil monotherapy, respectively); the G-Clb arm also demonstrated superior survival compared with that seen with chlorambucil monotherapy. Finally, there was an improvement in the rate of undetectable MRD with the addition of obinutuzumab versus rituximab (37.1% vs. 3.3% in blood and 19.5% vs. 2.6% in bone marrow). Achievement of undetectable MRD strongly correlated with PFS in the G-Clb group. Similarly, the COMPLEMENT 1 study compared chlorambucil to chlorambucil plus the CD20 monoclonal antibody ofatumumab (O-Clb) and demonstrated significantly longer PFS (median, 22.4 vs. 13.1 months), but not survival, with the O-Clb arm.\(^\text{72}\)

Finally, the RESONATE II study compared chlorambucil to the Bruton’s tyrosine kinase inhibitor ibrutinib in older patients (age ≥ 65).\(^\text{21}\) This study demonstrated a superior response rate, longer PFS, in treatment-naïve patients (median not reached in ibrutinib-treated patients; HR for progression or death, 0.09) and improved overall survival for patients initially treated with ibrutinib (HR 0.16). Also noteworthy is that, in the first-line setting, ibrutinib appeared to overcome the negative prognostic impact of del(11q) and unmutated IGHV.\(^\text{22}\) Ibrutinib is associated with two unique adverse effects of particular significance in older patients: atrial fibrillation and hemorrhage. In three randomized studies, the atrial fibrillation incidence was 5% to 7.7%, which was higher than that seen in the control arms (0.5% 2.4%).\(^\text{21,73,74}\) The incidence may continue to increase with time (up to 16% in longer-term follow-up).\(^\text{75}\) This adverse effect is noteworthy when ibrutinib use is considered in older patients, because atrial fibrillation risk increases in older adults in the general population.\(^\text{76,79}\) Bleeding risk is increased in ibrutinib-treated patients, although most bleeding is grade 1 or 2 mucocutaneous bleeding. In ibrutinib-treated patients, use of anticoagulants in atrial fibrillation is complicated by the known antiplatelet effects of ibrutinib.\(^\text{80,81}\) In addition, older, frail patients may be at risk for falling and so may have an increased risk of bleeding (e.g., subdural hematoma). Cross-study comparison suggests a markedly longer PFS with ibrutinib compared with G-Clb or O-Clb.\(^\text{82}\) Thus, although there are no head-to-head comparative data, we would favor ibrutinib instead of G-Clb or O-Clb unless comorbidities or financial considerations precluded the use of ibrutinib. Also, several ongoing studies are comparing novel regimens with chlorambucil/obinutuzumab: the ELEVATE-TN study (NCT02242942) is comparing acalabrutinib or

Treatment of Patients Ineligible for Fludarabine-Based CIT

Historically, patients ineligible for fludarabine-based CIT have been the most challenging to treat. For many years, before the availability of novel, targeted agents, the standard of care for older, unfit patients was chlorambucil because of the poor tolerability of fludarabine-based combination treatment, and because fludarabine monotherapy did not lead to distinct benefits compared with benefits from chlorambucil in the CLL8 study.\(^\text{69}\)

However, this paradigm has changed rapidly in recent years. Building on the data from CLL8 that the addition of the CD20 monoclonal antibody rituximab to FC improved PFS and survival in fit patients,\(^\text{10}\) the GCLLSG CLL11 study compared chlorambucil to chlorambucil plus rituximab (R-Clb) or chlorambucil plus obinutuzumab (G-Clb) in unfit patients (CIRS score > 6 or GFR < 70 mL/min/1.73m²).\(^\text{50}\) Obinutuzumab is a second-generation CD20 monoclonal antibody that is glycoengineered to enhance antibody-dependent cellular cytotoxicity.\(^\text{71}\) A total of 781 patients were randomly assigned across three arms. Both CD20 monoclonal antibody chemotherapy combinations demonstrated superior PFS relative to that seen with chlorambucil monotherapy (median PFS, 26.7 vs. 16.3 vs. 11.1 months, for G-Clb vs. R-Clb vs. chlorambucil monotherapy, respectively); the G-Clb arm also demonstrated superior survival compared with that seen with chlorambucil monotherapy. Finally, there was an improvement in the rate of undetectable MRD with the addition of obinutuzumab versus rituximab (37.1% vs. 3.3% in blood and 19.5% vs. 2.6% in bone marrow). Achievement of undetectable MRD strongly correlated with PFS in the G-Clb group. Similarly, the COMPLEMENT 1 study compared chlorambucil to chlorambucil plus the CD20 monoclonal antibody ofatumumab (O-Clb) and demonstrated significantly longer PFS (median, 22.4 vs. 13.1 months), but not survival, with the O-Clb arm.\(^\text{72}\)

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Acalabrutinib/obinutuzumab with chlorambucil/obinutuzumab in patients age 65 or older or younger than age 65 with either estimated GFR less than 70 mL/min/1.73m² or CIRS greater than 6 (which indicates ineligibility for FCR per GCLLSG criteria). The CLL14 study (NCT02242942) is comparing obinutuzumab/chlorambucil with venetoclax/chlorambucil. These two studies will likely raise the bar for treatment of patients with CLL who are older and less fit.

We now have active regimens capable of achieving durable responses in older patients with CLL. Initial treatment decisions should be made on the basis of prognostic factors and patient fitness. A general approach to the treatment of older patient is outlined in Figure 1. This figure considers only currently approved (by the U.S. Food and Drug Administration) treatment approaches; all patients, if eligible, should be considered for clinical trials.

**OPTIMAL SEQUENCING OF NEW MOLECULES IN THE TREATMENT OF CHRONIC LYMPHOCYTIC LEUKEMIA**

The therapeutic landscape for patients with CLL is in the midst of an exciting transformation: multiple novel agents have been approved since 2013. Although this is welcome news to patients, new challenges about how to best sequence these therapies and how to manage patients who experience relapse on these new molecules have emerged.

Sequencing in this contemporary era has not been well studied. Few prospective studies have compared novel agents to clinically relevant controls, and follow-up details after patient data are censored is lacking. Data about sequencing have been extrapolated from retrospective cohort studies and observational registries.

**First-Line Therapy**

The most important decision in managing CLL is determining whether therapy is warranted. Up to one-third of patients with CLL will never require treatment. Indications for therapy are defined by the international workshop on CLL. When indicated, treatment should be personalized and must consider patient fitness, goals of care, organ function, and the molecular-genetic prognostic profile. Standard first-line therapies include CIT combinations, anti-CD20 monoclonal antibodies, and ibrutinib monotherapy. Treatment options for initial therapy of CLL have already been discussed.

**Gaps in Knowledge for the Front Line**

Whether ibrutinib is superior to FCR or BR in the frontline setting remains unknown. This is of particular importance in patients with mutated IGHV and intact TP53, who benefit most from CIT. This question might be answered in the study that compares FCR with ibrutinib plus rituximab, which recently reached accrual and closed (NCT02048813). Another study that compares BR with ibrutinib plus rituximab or ibrutinib monotherapy (NCT01886840) will help answer this question in patients older than age 65.

**Relapsed/Refractory Setting**

Clonal evolution in CLL is observed in up to 50% of patients with relapsed disease. Thus, understanding the risk profile at relapse is critical for treatment selection. Data about sequencing after frontline ibrutinib comes mostly from a multicenter retrospective study of 391 patients. In this series, 24% (94 patients) discontinued ibrutinib. After

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**FIGURE 1. One Suggested Schematic for Treatment of Older Patients With Chronic Lymphocytic Leukemia According to Currently Available Therapies**

*Fit is defined as CIRS score of 6 or less and an eGFR of 70mL/min/1.73m² or greater.

†FCR is preferred instead of BR in patients with favorable genomic risk who are predicted to tolerate FCR, given the proven potential to achieve very-long-term remissions in this patient population.

‡Ibrutinib is preferred instead of G-Clb or O-Clb for this population on the basis of cross-study comparative data, unless comorbidities or financial considerations preclude its use.

Abbreviations: BR, bendamustine and rituximab; G-Cl, obinutuzumab + chlorambucil; FCR, fludarabine, cyclophosphamide, rituximab; FISH, fluorescence in situ hybridization; O-Clb, ofatumumab + chlorambucil.
In relapsed disease, idelausib and rituximab had superior ORR (81% vs. 13%; p < .001), PFS (median, not reached vs. 5.5 months; 93% vs. 46%; HR 0.15; p < .001), and OS (92% vs. 80% at 12 months; HR 0.28; p = .02) compared with rituximab. Patients were heavily pretreated (median of three prior therapies), had high risks [42% del(17p) or TP53 mutated], and had important medical comorbidities (median CIRS score, 8).

In the RESONATE study, ibrutinib was compared with ofatumumab, and ibrutinib resulted in significant improvements in ORR (42.6% vs. 4.1%; p < .001), PFS (not reached vs. 8.1 months; HR 0.22; p < .001), and OS (90% at 12 months vs. 81%; HR 0.43; p = .005). Ibrutinib also has been studied in 144 patients with del(17p) relapsed CLL (39% received three or more prior therapies) and resulted in 24-month PFS and OS rates of 63% and 75%, respectively.

Venetoclax was effective in all risk categories, including del(17p) CLL (ORR, 71%), heavily pretreated (at least four prior therapies; ORR, 73%), bulky disease (ORR, 78%), unmutated IGHV (ORR, 76%), and fludarabine-resistant disease (ORR, 79%). In a phase II dose-escalation study in 116 patients with relapsed CLL who were treated with venetoclax, the ORR was 79%, the 15-month PFS was 69%, and the 2-year OS was 84%. Venetoclax was effective in all risk categories, including del(17p) CLL (ORR, 71%), heavily pretreated (at least four prior therapies; ORR, 73%), bulky disease (ORR, 78%), unmutated IGHV (ORR, 76%), and fludarabine-resistant disease (ORR, 79%). In a phase II study with 107 patients who had relapsed del(17p) CLL, venetoclax demonstrated a 79% ORR and estimated 12-month PFS and OS rates of 72% and 86.7%, respectively.

In relapsed disease, venetoclax and rituximab demonstrated a superior PFS response compared with that seen with BR in the relapsed setting (MURANO trial; estimated 24-month PFS, 84.9% vs. 36.3%). No comparative prospective studies have been conducted to confirm which small molecules are best in patients who experience disease progression or relapse after CIT. In an attempt to answer this question, results of a retrospective analysis suggested that ibrutinib is superior to ideelasib-based therapy in relapsed disease, even in patients with del(17p) and complex karyotype. Although these data are retrospective, they support the use of ibrutinib as the first B-cell receptor inhibitor across multiple treatment settings.

Data on the best approach upon second relapse are limited. A research group from The Ohio State University showed that up to 51% of 308 patients enrolled in clinical trials may discontinue ibrutinib within the first 4 years after treatment initiation. In a real-world series of 621 ibrutinib-treated patients, (median follow-up, 14.5 months) the ibrutinib discontinuation rate was 42% (median time to discontinuation, 7 months). Current evidence suggests that venetoclax is the best approach in patients whose disease fails to respond to a B-cell receptor inhibitor (particularly in the setting of CLL progression).

**Proposed Sequencing Recommendations in Relapsed Disease**

- B-cell receptor inhibitor-naive patients with or without del(17p): ibrutinib, ideelasib/rituximab, or venetoclax are all viable choices, with the caveat that venetoclax is approved in the United States only for patients with del(17p). Recently reported clinical trial data and two real-world evidence series demonstrated the activity of venetoclax in patients who experienced progression during or after treatment with a B-cell receptor inhibitor. Data to support a sequence in which venetoclax precedes ibrutinib are promising but minimal and are limited to two retrospective series.

- B-cell receptor inhibitor-treated patients/those who discontinued treatment because of progression: We suggest venetoclax as the next line of therapy. However, we note that, in patients without del(17p), this is an off-label recommendation. Venetoclax monotherapy has been studied prospectively in patients who experience relapse during treatment with a B-cell receptor inhibitor and has demonstrated an ORR of 65% to 67% as well as median PFS times of 24.7 months (in the cohort with prior ibrutinib treatment) and not reached (in the cohort with prior ideelasib treatment).

- B-cell receptor inhibitor-treated patients/those who discontinued treatment because of toxicity: Recent data demonstrate that adverse events are a major reason for discontinuation of B-cell receptor inhibitors. Although prospective studies in patients intolerant to B-cell receptor inhibitors are ongoing (NCT02717611, NCT02742090), preliminary data suggest that the durability of responses are maintained when treatment is switching between B-cell receptor inhibitors in the setting of intolerance.

Venetoclax also is active and can be considered. Figure 2 proposes an algorithm to best sequence current therapies in CLL.

**CONCLUSION**

Chemotherapy still has a viable role in the treatment of CLL. Small molecules generally have an advantage in patients with relapsed disease; however, data in the frontline setting suggest a potential cure in the subset of patients with a mutated IGHV gene who receive FCR. The oral inhibitors appear to be the treatment of choice for older patients who are less likely to be able to tolerate the more effective chemotherapy.
FIGURE 2. Proposed Sequencing Approach: Combined Frontline and Relapsed/Refractory Settings

Newly diagnosed CLL patient requiring therapy by the iwCLL criteria

Intact TP53

IGHV mutated, fit, age <65 years, and GFR >70 ml/min; CIRS <6

IGHV mutated, unfit or high CIRS

IGHV unmutated

Ibrutinib

Ibrutinib discontinuation

Due to intolerance

Due to progression

Ibrutinib (preferred), obinutuzumab + chlorambucil

BR, ibrutinib, obinutuzumab + chlorambucil

Recheck FISH and TP53 mutation

If CIT given first line: ibrutinib preferred. Idelalisib-rituximab if not ibrutinib candidate. Consider venetoclax if del17p acquired.

If ibrutinib first line:
- Reason for discontinuation was intolerance: Idelalisib + rituximab or venetoclax. Utility of CIT remains unstudied.
- Reason for discontinuation was progression: Venetoclax (preferred), idelalisib + rituximab. Utility of CIT remains unstudied.

Consideration of venetoclax or idelalisib + rituximab, CIT (last option)

Venetoclax (if given idelalisib + rituximab)

Consideration of allo transplant if fit

Venetoclax (preferred), idelalisib + rituximab, CIT (last option)

Consideration of allo transplant if fit

*Evaluate for clinical trial at each sequencing step
*Cumulative Illness Rating Scale
*Use is off label in US if patient does not have 17p deletion and prior therapy. Please see EMA SMPC for additional indications in the EU.
*Allogenic stem cell transplant
regimens (e.g., FCR or BR). Realistically, use may be limited in the United States because of high copays and in Europe by the ability to prescribe these agents as initial therapy (also related to cost). Finally, in the setting of treatment discontinuation because of toxicities, outcomes after switching to an alternate B-cell receptor inhibitor or to a BCL2 inhibitor appear favorable. However, in the setting of resistance to a B-cell receptor inhibitor; switching to a BCL2 inhibitor is a better strategy. Lacking at this point in time are data for what will be effective in the setting of resistance to venetoclax. This incomplete data partly reflects the poorly defined mechanisms of resistance. In addition, because venetoclax was relatively recently approved, little data about post-venetoclax therapy exist. Multiple small molecules are being investigated in clinical trials; these include SYK, Bruton’s tyrosine kinase, and PI3K inhibitors. Thus, the expectation is that next-generation small molecules will become available soon; we welcome these advances in the treatment of CLL and at the same time strive to develop logical algorithms for the incorporation and sequencing of oral inhibitors.

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Nivolumab and pembrolizumab are the first two U.S. Food and Drug Administration (FDA)–approved monoclonal antibodies targeting PD-1. The engagement of the PD-1 receptor to its ligand (PD-L1) on tumoral cells and tumor-driven antigen-presenting cells blocks T-cell receptor signaling and T-cell response, leading to T-cell exhaustion. Nivolumab and pembrolizumab block the interaction between PD-1 and PD-L1, releasing the brake on antitumoral T cells (Fig. 1). These drugs have earned a series of FDA approvals across all solid tumors, frequently based on PD-1 expression, rather than cancer site.

CHECKPOINT INHIBITORS IN LYMPHOMA: WHEN AND HOW

The activity of nivolumab and pembrolizumab has also been investigated in patients affected by different types of lymphoma, with discrepant results between Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) in the initial phase I studies. The CheckMate 039 trial enrolled 23 patients with extensively pretreated relapsed refractory classic HL (cHL), including 78% who had received prior autologous stem cell transplantation and/or brentuximab vedotin (BV). Nivolumab was given at a dose of 3 mg/kg every 2 weeks, resulting in an overall response rate (ORR) of 87%, a complete response (CR) rate of 19%, and 1-year progression-free survival (PFS) rate of 46%; grade 3 adverse events (AEs) were reported in 22% of patients (mostly immune-mediated), but no grade 4 AEs were observed. The Keynote 013 trial included 31 patients with heavily pretreated cHL; BV had failed in all patients, and disease had relapsed in 71% after autologous stem cell transplantation. Pembrolizumab was given at a dose of 10 mg/kg every 2 weeks and resulted in an ORR of 65% and a CR rate of 16%. Grade 3 AEs were reported in 16% (mostly immune-mediated), and no grade 4 AEs were observed. The results of a phase I study of nivolumab (but not pembrolizumab) for the treatment of patients with relapsed NHL (including B- and T-cell lymphomas) have been reported, and ORR was far more modest, ranging between 15% and 40%.
Given the promising activity of these immune therapy agents in cHL, confirmatory studies have been performed. The CheckMate 205 study is the phase II registration study investigating the efficacy of nivolumab in patients with relapsed HL, and results have been reported for one of the four arms, including 80 patients who had progressed after both BV and autologous stem cell transplantation; the study used the same regimen as in the original phase I trial. The ORR was 66%, the CR rate was 9%, and median PFS was not reached at 15 months.6 Keynote 087 is the phase II registration study of pembrolizumab for the treatment of patients with relapsed HL. The design was similar to that of CheckMate 205, including three arms based on previous exposure to BV and/or autologous stem cell transplantation, and results from all 32 cohorts have been reported. With use of a different dosing strategy (200 mg intravenously every 3 weeks) than in the original phase I study, the ORR was 69%, the CR rate was 22%, and median PFS had not yet been reached. Of interest, similar response rates were observed among primary refractory and relapsed disease.7

A small portion of patients enrolled in the above-mentioned studies have experienced an initial increase in tumor size or appearance of new lesions but subsequent decrease in overall tumor burden. These findings of “pseudoprogression,” likely secondary to the expansion of an antitumoral inflammatory infiltrate, would be classified as progressive disease by the Revised Response Criteria for malignant lymphomas, but not by the Immune-Related Response Criteria, which requires a confirmation of progression on two consecutive observations at least 4 weeks apart.8 Relevant to this, 70 patients in CheckMate 205 study were treated with nivolumab beyond progression (defined by radiographic response criteria), and 30% have an ongoing response, with a median time to next treatment of 17 months; these findings highlight the need for the use of revised response criteria for lymphomas in the era of immunotherapy.9,10

Because high levels of PD-L1 have been associated with poor outcomes in patients with chL treated with chemotherapy, the combination of the latter with PD-1 inhibitors has been investigated.11 Cohort D of the CheckMate 205 study included patients with newly diagnosed advanced-stage chL who, after frontline treatment with four cycles of nivolumab (at 240 mg as fixed dose every 2 weeks), received six cycles of the combination of nivolumab and doxorubicin, vinblastine, and dacarbazine; this regimen resulted in an ORR of 86% and a CR rate of 80% and was well tolerated.12

In addition, chemotherapy-free combinations of immunotherapy have been investigated for the treatment of patients with chL. A phase I trial of nivolumab and BV in patients with relapsed refractory chL resulted in an ORR of 82% and a CR rate of 61%.13 Given this efficacy and manageable safety profile, a phase I trial evaluating nivolumab
and BV as frontline treatment of elderly patients with HL not eligible for chemotherapy (NCT02758) is underway. The combination of nivolumab, ipilimumab (an anti–CTLA-4 monoclonal antibody), and BV has resulted in an impressive ORR of 100% and CR rate of 63% in a similar population, with a manageable toxicity profile.\textsuperscript{14}

In cHL, 9p24.1 amplification is a frequent genetic abnormality, leading to increased expression of PD-L1 on lymphoma cells, both directly and as a consequence of JAK2 pathway activation, likely explaining the efficacy of PD-L1 inhibitors in these patients.\textsuperscript{11,15} As opposed to cHL, PD-L1 expression is variable in NHL, likely resulting in the more modest results achieved thus far with the use of immunotherapy in these patients. PD-L1 overexpression has been reported in only 10% to 20% of aggressive B-cell NHL, mostly non-germinal center subtype.\textsuperscript{16} However, abnormalities in chromosome 9p, leading to PD-L1 overexpression through a mechanism similar to that described in cHL, are observed in more than 50% of patients with primary mediastinal B-cell lymphoma and mediastinal gray zone lymphomas, making these two NHL subtypes optimal candidates for immunotherapy-based clinical trials.\textsuperscript{15,17} Nonetheless, immune escape pathways may play a critical role in the pathogenesis, especially in MYC-driven tumors.\textsuperscript{18} In addition, the accuracy of PD-L1 expression as a predictor of response to immunotherapy remains debated both in c-HL and NHL, and alternative biomarkers, such as gene expression profile and tumor immune infiltrate composition, are being investigated.\textsuperscript{4,19}

To date, the most promising results with PD-L1 blockade in NHL have been observed in NHL subtypes with higher expression of PD-L1. A phase I trial of pembrolizumab for the treatment of patients with relapsed refractory primary mediastinal B-cell lymphoma has shown an ORR of 41%, with prolonged response duration in most patients.\textsuperscript{20} Four of nine treated patients with Richter syndrome have shown response to pembrolizumab, with a median PFS of 5 months\textsuperscript{21}; all four treated patients with primary central nervous system lymphoma have achieved response with nivolumab, with responses ongoing in three patients.\textsuperscript{22} Trials of combinations of pembrolizumab with chemotherapy (NCT02541565) or vorinostat (NCT03150329) are under evaluation. Nivolumab and pembrolizumab have also been investigated for the treatment of patients with aggressive T-cell lymphomas, with ORRs ranging between 15% and 40% and the highest responses observed in natural killer/T-cell subtypes.\textsuperscript{5,23,24} A trial of the combination of pembrolizumab with romidepsin (NCT03278782) is now actively recruiting (Table 1).

Results have been less impressive in indolent NHL, with only four of 20 patients responding to nivolumab in the initial phase I study.\textsuperscript{3} However, when combined with rituximab in patients with relapsed follicular lymphoma (FL), the ORR was 67% and CR rate was 50%.\textsuperscript{25} A trial investigating the combination of nivolumab with ibrutinib oridelalisib (NCT02332980) is ongoing. In indolent NHL, combination studies are likely to overcome the modest activity observed.

### TABLE 1. Actively Recruiting Trials of Immunotherapy in Lymphoma

<table>
<thead>
<tr>
<th>Clinical Trial Number</th>
<th>Patient Population</th>
<th>Study Phase</th>
<th>Regimen</th>
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<tbody>
<tr>
<td>NCT03035331</td>
<td>Relapsed NHL</td>
<td>Phase II</td>
<td>Pembrolizumab + dendritic cell therapy</td>
</tr>
<tr>
<td>NCT02650999</td>
<td>Relapsed B-NHL</td>
<td>Phase I/Ii</td>
<td>Pembrolizumab + anti-CD19 CAR T-cell therapy</td>
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<td>Pembrolizumab + chemotherapy</td>
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<td>Durvalumab + R-CHOP or lenalidomide + R-CHOP</td>
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<td>Avelumab</td>
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Abbreviations: NHL, non-Hodgkin lymphoma; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; BV, brentuximab vedotin; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; PTCL, peripheral T-cell lymphoma.
with single-agent PD-1 blockade. Given the mechanism of action, PD-L1 inhibitors may also improve the efficacy of cellular therapy, and their combinations with intratumoral immunotherapy (NCT02677155), dendritic cell therapy (NCT03035331), and chimeric antigen receptor (CAR)–modified T-cell therapy (NCT02650999) are being investigated.

Checkpoint inhibitors other than nivolumab and pembrolizumab are also being investigated in lymphoid malignancies. As outlined above, the addition of the CTLA-4 inhibitor ipilimumab resulted in improvement in response rates when combined with nivolumab, suggesting that combined checkpoint inhibitors may result in enhanced efficacy.\(^26,27\) The combination of atezolizumab, a PD-L1 inhibitor, with obinutuzumab and bendamustine has resulted in an ORR of 85% and a CR rate of 75% in a population of patients with heavily pretreated FL.\(^28\) Atezolizumab in combination with emactuzumab, a colony-stimulating factor 1 receptor inhibitor targeting tumor-associated macrophages (NCT03369964), is ongoing. Recruiting trials with other PD-L1 inhibitors include durvalumab plus chemotherapy with or without lenalidomide (NCT03003520) or with CAR T-cell therapy (NCT02706405), and single-agent avelumab for the treatment of relapsed refractory HL (NCT02603419) or T-cell lymphoma (NCT03046953).

Immunotherapy is associated with a manageable safety profile and is an effective treatment in patients with relapsed HL. Combination studies with chemotherapy, other biologic agents, and cellular therapy, as well as use in untreated patients, appear promising. More modest activity has been observed with single-agent PD-L1 antibodies in most NHL subtypes. Ongoing studies aimed at improving efficacy with combination strategies, designed to enhance synergism, will be required for further development of immune therapy in NHL.

CD19 CAR T CELLS FOR NON-HODGKIN LYMPHOMA

CAR-modified T cells have demonstrated efficacy as an adoptive cell therapy for relapsed disease and hematologic malignancies in high-risk patients after hematopoietic stem cell transplant. Major advantages of CAR T cells include their recognition of both protein and nonprotein targets, their ability to migrate to tumor sites, demonstration of in vivo expansion and persistence, high specificity to prevent off-target adverse effects, and the capacity to overcome tumor escape from low antigen presentation or HLA expression, through HLA-independent recognition.\(^29,30\)\) CARs possess two critical main components. First, the extracellular recognition domain, typically derived from antibody-variable regions, recognizes the desired target to provide signal 1.\(^31\) Second, the extracellular domain is coupled to an intracellular signaling domain to provide signal 2, often multiple costimulatory domains to generate T-cell activation.

The clinical applications of CAR-modified T cells have been demonstrated with the remarkable success of CD19-modified CAR T cells for patients primarily with common CD19+ B-cell malignancies, including acute lymphoblastic leukemia (ALL) and NHL.\(^32-34\) NHL includes malignancies that arise from T-cell, B-cell, and natural killer cell lineages, allowing common proteins expressed on these cell types to be used as targets of immunotherapy. For example, CD19 is expressed throughout all stages of B-cell differentiation and is overexpressed in B-cell malignancies.\(^35\) As such, CD19 CAR T-cell therapy is an attractive treatment strategy for B-cell NHL, with several clinical trials in progress and one product receiving licensure for the NHL indication. Despite the recent successes with CAR T-cell clinical trials, major concerns associated with this therapy include cytokine release syndrome (CRS), potential neurotoxicity, B-cell aplasia, and loss of tumor antigen leading to relapse. These adverse effects must be weighed against the advantages of CAR T-cell therapy to determine the optimal course of treatment of patients with cancer, with the ultimate goal of preventing relapse and resistance.\(^36\)

CD19 CAR T cells for B-cell malignancies such as NHL have progressively improved as CAR constructs have evolved through multiple generations to improve signal 2, intracellular costimulatory signaling. First-generation CD19 CAR T cells for CD19+ B cell malignancies were met with limited efficacy in preliminary trials because of sole inclusion of a single intracellular signaling domain, TCR zeta chain, without a costimulatory domain.\(^37\) These initial therapies by City of Hope Medical Center demonstrated limited persistence in circulation (1–7 days), with poor clinical efficacy.

Subsequent studies with second-generation CARs included additional costimulatory domains, CD28 or 4-1BB, in an attempt to improve persistence in vivo and enhance antitumor efficacy. To demonstrate the advantages provided by costimulatory domains in CAR design, Savoldo and colleagues at Baylor College of Medicine infused patients with NHL or chronic lymphocytic leukemia with a first-generation CD19 CAR lacking a costimulatory domain or a second-generation CD19 CAR with a CD28 costimulatory domain (CD28z).\(^38\) Patients infused with the second-generation CD19-(CD28z) CAR had enhanced in vivo expansion and persistence of CAR T cells compared with those infused with CD19 CAR lacking a costimulatory domain. In tandem, a group at the National Cancer Institute (NCI) infused CD19-(CD28z) CAR T cells constructed with the scFv FMC63 into a patient with FL. The patient received 7 days of conditioning with cyclophosphamide (Cy; 60 mg/kg) and fludarabine (Flu; 25 mg/m2) to achieve adequate lymphodepletion to eliminate competing endogenous lymphocytes.\(^39\) After T-cell infusion, the patient achieved a partial response, with dramatic regression of the lymphoma after CD19 CAR T-cell infusion with an absence of B cells in the circulation for 39 weeks and low serum immunoglobulin levels, reflecting eradication of the B-cell lineage.\(^39\)

This group then went on to treat nine patients with aggressive NHLs (primary mediastinal B-cell lymphoma and diffuse large B-cell lymphoma [DLBCL]); five of nine patients achieved a CR (6–35+ months’ duration).\(^40\) However, grade 3 or greater toxicities occurred in 100% of patients, including grade 5 toxicities. Therefore, in their subsequent trial, patients received only 3 days conditioning with Flu/Cy, which
dramatically reduced the toxicity rate; grade 3 to 4 neurotoxicity developed in 55% of patients and grade 3 to 4 hypotension developed in only 18%. There were no deaths and all toxicities resolved within 2 weeks. Furthermore, despite the reduction in severe adverse events, of the 19 patients treated, the CR rate was maintained at 55%. In addition to patients with DLBCL who achieved a CR rate of 47%, this study also included one patient with mantle cell lymphoma and two patients with FL, all of whom achieved a CR.41

The Fred Hutchinson Cancer Research Center subsequently conducted a trial to treat patients with NHL by using CD19-(4-1BB) CAR T cells in a 1:1 ratio of CD4+:CD8+ T cells.42 Thirty-two adults with relapsed and/or refractory NHL underwent lymphodepletion with cyclophosphamide with or without combination with fludarabine, followed by CD19-(4-1BB) CAR T-cell infusion. The researchers found that patients who received Cy/Flu-combined lymphodepletion had improved response rates (50% CR; 75% ORR) compared with patients who received Cy alone (8% CR; 50% ORR).42 The Cy/Flu combination minimized the immune response to the murine scFv on the CD19-(4-1BB) CAR, allowing for improved CAR T-cell expansion and subsequent PFS compared with the Cy-alone patients. Similar to the NCI trial, severe CRS and neurotoxicity were observed in 28% of all patients, emblematic of the challenges with CD19 CAR T-cell therapies for B-cell malignancies.

The group from the University of Pennsylvania also used the CD19 CAR, which included 4-1BB instead of CD28 as the costimulatory domain, to treat patients with DLBCL.43 Moreover, all patients had “double hit” DLBCL, defined by specific chromosomal breaks from FL transformation in the following loci: MYC/Bq24, BCL2/18q21, and/or BCL6/3q27. A total of 12 patients received varying “dealer’s choice” lymphodepleting conditioning regimens followed by infusion of CD19-(4-1BBz) CAR T cells. The ORR was 52% (7/13) for all patients in this double-hit lymphoma trial, with a CR rate of 46% (6 of 13).43

Several multicenter industry-sponsored trials (Table 2) have been developed from these key studies conducted in the academic setting (Fig. 2). ZUMA-1 (NCT02348216)44 was a Kite-sponsored phase I trial in which autologous CD19-(CD28z) CAR T cells (developed by the NCI group) were infused into seven patients with refractory DLBCL after Cy/Flu conditioning chemotherapy. The ORR was 71% (5 of 7), with a CR of 57% (4 of 7); three patients had ongoing CR at 12+ months, and CD19 CAR T cells were still detectable at 12+ months. One of seven patients experienced CRS and neurotoxicity developed in four. The phase II ZUMA-1 trial enrolled 101 patients with DLBCL, transformed FL, or primary mediastinal B-cell lymphoma. Patients received lymphodepleting chemotherapy followed by a single CD19-CAR-(CD28z) T-cell infusion. The best ORR was 82%, with a CR rate of 54%. At 6 months the ORR was 41% and the CR rate was 36%.45,46

The Juno-sponsored study (TRANSCEND) used the T-cell product (JCAR017) developed at the Fred Hutchinson Cancer Center; in this study, CD19-(4-1BBz) CAR–transduced CD8+ and CD4+ T cells were infused at a 1:1 ratio. Sixty-eight patients with DLBCL and transformed FL received JCAR017 after lymphodepleting Flu/Cy chemotherapy. The best ORR was 75%, with a CR rate of 56% (68 patients). At 6 months (35 patients), the ORR was 40% and the CR rate was 37%; 1% of patients had grade 3 or higher CRS and 14% had grade 3 or higher neurotoxicity.47

Finally, the Novartis-sponsored phase II trial, JULIET (NCT02445248), was conducted with CD19-(4-1BBz) CAR T cells (first evaluated at the University of Pennsylvania) in adult patients with relapsed or refractory DLBCL.48 A total of 147 patients were enrolled, and 99 received a single-dose infusion of CD19 CAR T cells after lymphodepleting chemotherapy with Cy/Flu or bendamustine. The best ORR was 53.1%, with a CR rate of 39.5% (81 patients). Participants evaluated at 6 months (46 patients) showed 37% ORR, 30% CR, and 7% partial response, as well as detection of CD19-(4-1BB) CAR T cells for up to 367 days.48 CRS occurred in 58% of patients, with 86% reporting grade 3 or 4 AEs, including neurotoxicity. No deaths were attributed to CD19 CAR T-cell infusion, CRS, or neurotoxicity, despite the high AE rate, which may in part be due to differences in the grading systems used in the studies.48

In summary, these promising phase I and II studies demonstrate that CD19 CAR T cells for NHL are a promising strategy to achieve tumor regression. However, the best strategy to develop the optimal therapy for patients remains unclear as studies vary in CAR design and dosage, lymphodepleting strategies, and tumor burdens of participants.

CHALLENGES WITH CD19 CAR T-CELL THERAPIES

Overcoming Toxicity

CRS, neurotoxicity, macrophage activation syndrome, B-cell aplasia, and autoimmune toxicity (on-target, off-tumor effects on healthy tissues) remain challenges with CD19 CAR T-cell therapy. B-cell aplasia results from autoimmune toxicity, or depletion of normal B cells expressing CD19, in addition to malignant cells. However, immunoglobulin infusions can mitigate the effects of B-cell aplasia.49 More serious AEs, such as CRS, occur from overactivation of the immune system, resulting in the unnatural release of large quantities of inflammatory cytokines.50,51 CRS results in a range of symptoms from fevers to the more serious respiratory distress, cardiac dysfunction, and even neurologic complications and can take days to weeks to appear after CAR T-cell infusion. The manifestation of these symptoms often coincides with in vivo CAR T-cell expansion.50 Current options to treat CRS include humanized monoclonal antibodies against interleukin (IL)-6, such as tocilizumab and siltuximab, which have demonstrated success in caring for patients with CRS.50,51 Signs of neurotoxicity and macrophage activation syndrome are generally self-limiting after infusion but are monitored closely in patients for severity. In addressing possible off-target effects from CAR T-cell therapies, several groups are looking at the inclusion of inducible suicide genes to enable controlled depletion of CAR T cells,52-54 (the EGFR tracking and suicide gene was used in the Juno TRANSCEND study),
which has succeeded in controlling graft-versus-host disease in patients after allogeneic bone marrow transplantation.55

**Overcoming Tumor Immune Evasion**

Tumor escape and immune editing are common methods of immune evasion. Tumors avoid recognition by the immune system through downregulation of the major histocompatibility complex and epigenetic downregulation of tumor-associated antigens, resulting in loss of expression. One of the problems associated with CD19 CAR T-cell therapy is tumor antigen loss, leading to relapse with a CD19-negative tumor.56,57 One approach to overcome tumor antigen loss is to use CARs targeting other extracellular antigens expressed by NHLs, such as CD20 and CD30.58,59 Another approach is to develop antigen-specific T-cell products targeting multiple tumor-associated antigens, including tumor-associated viral antigens and cancer testsis antigens.60-63 Clinical trials using multi–antigen-specific T cells for NHLs positive and negative for Epstein-Barr virus (beyond post-transplant lymphoproliferative disorder) have demonstrated similar CR rates of approximately 50% but without the severe toxicities observed with CD19-CAR T cells.64,65 Additionally, tumors secrete immunosuppressive cytokines, such as transforming growth factor-β (TGF-β), which recruit T regulatory cells and myeloid-derived suppressive cells to prevent immune activation and may lead to T-cell exhaustion.18,66,67 To overcome the immunosuppressive tumor microenvironment, T cells can be genetically engineered to be rendered resistant to, for example, the antiproliferative effects of TGF-β using a dominant negative TGF-β type II receptor that is nonfunctional. This creates a sink, binding TGF-β but with a blockade of the downstream signal transduction pathway.68-70

**PRACTICAL APPLICATIONS AND NEW TARGETS**

The many variables in the design of CAR T cells include antigen target, costimulatory domains, and transfection agents. Many groups are also working on novel designs to improve efficacy of CAR T-cell therapy. CAR T cells able to release inflammatory cytokines, such as IL-18, help to induce a Th1 acute phase immune response with M1 macrophages and natural killer cells to augment antitumor immunotherapy.71,72 Combination of IL-12 and doxorubicin improved CAR T-cell penetration and overall survival in murine models for lung and breast cancer.73 Generating CAR T cells that secrete anti–PD-1 checkpoint inhibitors improved T-cell survival and resulted in complete elimination of tumors in a lung murine model. Further, Foster and colleagues were able to control

<table>
<thead>
<tr>
<th>Trial Name/Trial ID</th>
<th>Methods</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>KITE; KTE-C19</td>
<td>CD19-(CD28z) CAR T cells + lymphodepleting Flu/Cy chemotherapy</td>
<td>7 patients with refractory DLBCL</td>
<td>71% ORR (5/7) 57% CR (4/7) 3 patients: ongoing CR at 12+ mo; CD19 CAR T cells still detectable to 12+ mo</td>
<td>1/7 CRS 4/7 neurotoxicity</td>
</tr>
<tr>
<td>ZUMA-1 Phase II</td>
<td>Single CD19-CAR-(CD28z) T-cell infusion + lymphodepleting Flu/Cy chemotherapy</td>
<td>Enrolled 101 patients with DLBCL, tFL, or primary mediastinal B-cell lymphoma</td>
<td>82% best ORR (n = 101) 54% CR 6-mo follow-up: 41% ORR, 36% CR</td>
<td>13% grade ≥ 3 CRS 28% grade ≥ 3 neurotoxicity</td>
</tr>
<tr>
<td>JUNO; JCAR017</td>
<td>CD19-(4-1BBz) CAR transduced CD8+ and CD4+ T cells were infused with JCAR017 at a 1:1 ratio + lymphodepleting Flu/Cy chemotherapy</td>
<td>68 patients with DLBCL and tFL</td>
<td>75% best ORR 56% CR (n = 68) 6-mo follow-up (n = 35): 40% ORR, 37% CR</td>
<td>1% grade ≥ 3 CRS 14% grade ≥ 3 neurotoxicity</td>
</tr>
<tr>
<td>NOVARTIS; CT019</td>
<td>CD19-(4-1BB) CAR T cells: 99 participants received single-dose infusion of CD19 CAR T cells + lymphodepleting chemotherapy with Cy/Flu or bendamustine</td>
<td>147 patients enrolled with relapsed or refractory DLBCL</td>
<td>53.1% best ORR 39.5% CR (n = 81) 6-mo follow-up: (n = 46) 37% ORR, 30% CR, 7% PR Detection of CD19- (4-1BB) CAR T cells for up to 367 d</td>
<td>23% grade ≥ 3 CRS 13% grade ≥ 3 neurotoxicity</td>
</tr>
</tbody>
</table>

Abbreviations: CAR, chimeric antigen receptor; Flu, fludarabine; Cy, cyclophosphamide; DLBCL, diffuse large B-cell lymphoma; ORR, overall response rate; CR, complete response; CRS, cytokine release syndrome; tFL, transformed follicular lymphoma; PR, partial response.
the regulation of CAR T-cell expansion and survival by using rimiducid, a synthetic dimerizing ligand, to activate IL-2 production through MyD88/CD40. In addition, instead of using svFc domains, adnectin, a class of affinity molecules from fibronectin, is being evaluated as the antigen-binding motif of CAR T cells, with similar efficacies toward lung cancer cell lines.

Clinical trials with CAR T-cell therapy have been promising in other hematologic malignancies. CD19 homing CAR T cells have been tested in patients with chronic lymphocytic leukemia at the University of Pennsylvania and Fred Hutchinson Cancer Research Center, with good response rates (ORR ranging from 39% to 71%). Garfall and colleagues at the University of Pennsylvania also tested their CD19-targeted CAR T cells for multiple myeloma (MM) in a pilot study; 10 patients showed peak bone marrow infiltration correlated with favorable PFS.

A major attractive property of CAR T cells is that the svFc domain can be changed to target various surface antigens. For example, B-cell mature antigen as the target for multiple myeloma has been tested by several groups, with a high response rate. Berdeja and colleagues showed that for the six evaluable patients with refractory/relapsed MM, the ORR was 100%, including two CRs and two minimal residual disease-negative responses. The LEGEND-2 trial in China using LCAR-B38M CAR T cells, which also target B-cell mature antigen, showed similar results; 22 patients with refractory/relapsed MM patients had a 100% ORR and 27% had minimal residual disease-negative CR. However, a similar clinical trial at NCI/National Institutes of Health using a different B-cell mature antigen–targeted CAR T cell (with a CD28 costimulatory domain) showed an ORR of only 30%. Newer targets are still being investigated for MM, such as active conformation of β7 integrin. Ramos and colleagues reported that nine patients (mainly younger 20- to 50-year-olds) treated with anti-CD30 CAR T cells for HL had a 33% CR, 33% had stable disease, and 33% had no response. The longest-responding patient has had no evidence of disease for more than 3 years.

Unlike the success of CAR T-cell therapy in ALL and NHL, its use (with first-generation T cells) for solid tumors has not been effective thus far. In contrast to the experience with hematologic malignancies, CAR T-cell therapy for solid tumors exposes two major difficulties. First is the relative

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FIGURE 2. Industry-Sponsored CD19 CAR Constructs

Abbreviations: 3′LTR, 3′-long terminal repeat; 5′LTR, 5′-long terminal repeat; ALL, acute lymphocytic leukemia; CHOP, Children’s Hospital of Philadelphia; DLBCL, diffuse large B-cell lymphoma; FHCRC, Fred Hutchinson Cancer Research Center; MSKCC, Memorial Sloan Kettering Cancer Center; NHL, non-Hodgkin lymphoma.
inability of CAR T cells to penetrate a solid tumor, which often has a specialized extracellular matrix that can limit T-cell infiltration and has developed an immune-tolerant tumor microenvironment. Second, unlike patients with ALL or NHL, who are often heavily treated with chemotherapy regimens that deplete lymphocytes, providing a favorable milieu for CAR T-cell therapy, patients with solid tumor are often receiving lymphodepleting chemotherapies for the first time when enrolled in a CAR T-cell trial. However, as CAR T-cell designs have improved, clinical trials targeting solid tumors are still ongoing. Several of these trials are tumor agnostic, meaning that as long as the targeted antigen is expressed on the cancer cells, the origin of the cancer cells (gastrointestinal or breast) is not a specific criterion for the trials.

Mesothelin is a cell surface glycoprotein and is overexpressed in many thoracic malignancies, including 80% to 90% of mesotheliomas, 40% to 60% of lung adenocarcinomas, 40% of esophageal cancers, and 79% of thymic cancers. Mesothelin is also expressed on triple-negative breast, pancreatic, ovarian, and cervical cancer. Investigators at the University of Pennsylvania built a phase I clinical trial with preclinical studies using messenger RNA electroporation to allow transient antisenseolitin CAR T-cell therapy. Zeltsman and colleagues at Memorial Sloan Kettering Cancer Center showed in preclinical studies that local or intrapleural delivery of CAR T cells had a more potent and long-lasting response, leading to a phase I clinical trial. Many ongoing trials (NCT01355965, NCT01583686, NCT02159716, NCT02414269, NCT02580747, NCT02930933, NCT03054298) are using mesothelin-targeted CAR T cells; these trials are summarized in Table 3.

HER2 is a well-known breast cancer tumor marker and target for therapy. HER2 is also expressed in gastrointestinal stromal tumors, non–small cell lung cancer, and several other cancer types. Preclinical studies of trastuzumab-based CAR T cells were successful by producing cytotoxicity in various breast, ovarian, and pancreatic cancer cell lines and animal models. There was a case report of a patient receiving anti-HERB2 CAR T-cell therapy and had acute respiratory distress syndrome; the patient died 5 days after the infusion. Ahmed and colleagues reported a phase I anti-HER2-specific CAR T-cell trial with one patient who had a partial response persisting for longer than 9 months, seven patients with stable disease for 8 to 29 months, and eight patients who progressed despite CAR T-cell therapy. More clinical trials for anti-HER2 CAR T cells are mainly phase I (NCT01935843, NCT01022138, NCT02713984).

GD2 is a disialoganglioside that can be expressed on tumors of neuroectodermal origin, such as neuroblastoma, sarcoma, and melanoma. Louis and colleagues at Baylor College of Medicine found that three of 11 patients with neuroblastoma achieved a CR with anti-GD2 CAR T cells. They also noted that persistence of CAR T cells over 6 weeks had a favorable clinical outcome. Other clinical trials are using anti-GD2 CAR T cells for sarcoma, osteosarcoma, neuroblastoma, and melanoma (NCT02765243, NCT03373097, NCT02107963).

Carinoembryonic antigen (CEA) is commonly associated with colon cancer but can be seen with other malignancies, including lung, pancreatic, gastric, and breast carcinomas. A phase I study (NCT02349724) for anti-CEA CAR T cells for lung, colorectal, gastric, breast, and pancreatic cancers is continuing, and other phase I trials are focused on colorectal cancer. First-generation anti-CEACAM5-specific CAR T cells were found have limited efficacy because of poor persistence and transient preconditioning respiratory toxicity. EGFR mutation can be seen in 10% to 15% of lung adenocarcinomas. Two Chinese studies are evaluating the toxicities of anti-EGFR CAR T cells in multiple cancer types (NCT01869166, NCT02862028). Anti-VEGFR CAR T cells are also being evaluated in a phase I trial for metastatic melanoma and renal cancer (NCT01218867).

Other targets include ROR1 (NCT02706392) for NSCLC, breast cancer, and leukemias; MUC1 (NCT02587689) for triple-negative breast cancer, hepatocellular carcinoma, non–small cell lung cancer, and pancreatic cancer; GPC3 (NCT02876978) for non–small cell lung cancer (squamous cell carcinoma type); fibroblast activation protein for malignant pleural mesothelioma (NCT01722149); epithelial cell adhesion molecule for esophageal, pancreatic, and colon cancers (NCT03013712); and CD171, a cell adhesion molecule, for neuroblastoma (NCT02311621).

FEASIBILITY AND COST BURDEN OF CAR T-CELL THERAPY

After 2 decades and $200 million in government-supported research, the FDA approved tisagenlecleucel (Kymriah; Novartis) in August 2017 for ALL. This move has generated shock waves through the oncology community as we now have a new category of treatment options for an unfortunate disease that often affects children and young adults. More importantly, the potential does not end there. As mentioned previously, more CAR T-cell therapy research has stimulated interest in treating not only other hematologic malignancies but also solid tumors.

Novartis listed the price of the Kymriah to be $475,000. This cost does not include the cell collection, the lymphodepletion, the hospitalization, the other medications, or further clinic visits. The overall cost of the treatment can exceed $1 million. However, when the price is compared with that of the alternative treatment options, such as hematopoietic stem cell transplant (estimated to be $350,000–$800,000 by the American Cancer Society), Kymriah seemed less expensive, especially because that cost does not include economic impacts of stem cell banks, future hospitalizations for graft-versus-host disease complications, immune-suppression medications, or transfusions for cytopenias.

Soon after the approval of Kymriah, the FDA approved axicabtagene ciloleucel (Yescarta, Kite/Gilead) for adults with relapsed and/or refractory DLBCL. The price was listed at $373,00, which is almost $100,000 less than that of Kymriah. The American College of Cardiology and the American Heart Association attempt to standardize value for utilization. High value is considered less than $50,000 per quality-adjusted...
life year (QALY) added, and low value would be greater than $150,000. The Institute for Clinical and Economic Review released a report noting that Kymriah, in comparison with the control clofarabine, had an incremental cost-effectiveness ratio of approximately $46,000 per QALY gained. Yescarta had an incremental cost-effectiveness ratio of approximately $136,000 per QALY gained compared with standard chemotherapy. Both therapies were under $150,000 and thus was reported to be within reasonable pricing range.

The issue of cost not only causes a ripple effect on private insurers; in addition, the main burden would fall on Medicare and Medicaid reimbursement strategies, which link to taxes and government funding. Novartis offered to refund patients who relapse within 30 days, although almost 50% of patients in the trial relapse by 1 year. Novartis and Kite attempted to provide more supplementation and reimbursements in an attempt to alleviate the financial burdens, but the price is still steep. On top of the cost, accessibility is also an issue because these new therapies require special cellular Good Manufacturing Practices facilities, trained staff, and physicians who are comfortable managing a new set of side effects, such as CRS and neurotoxicity.

CONCLUSION

Overall, immunotherapy with checkpoint inhibitors and cellular therapy has given oncologists and patients hope where there used to be none, along with new toolboxes yet to come with further research and development. Checkpoint

### TABLE 3. Solid and Liquid Malignancies With More Than Two Target Antigen CAR T Cells in Clinical Trials (Other Than CD19, CD20, and CD22)

<table>
<thead>
<tr>
<th>Solid Malignancy</th>
<th>Lung</th>
<th>Gastric</th>
<th>Colorectal</th>
<th>HCC</th>
<th>Pancreatic</th>
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<tbody>
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<td>CD133</td>
<td>CD133</td>
<td>CD133</td>
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<td>CD70</td>
<td>MUC1</td>
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<td>EGFR</td>
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<tr>
<td>MSLN</td>
<td>EGFR</td>
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<table>
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<th>Liquid Malignancy</th>
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<td>CD133</td>
<td>LewisY</td>
<td>BCMA*</td>
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<td>NKG2D</td>
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<td>CD33</td>
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<td>NKG2D</td>
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</table>

*Corresponding clinical trials can be found by searching the target, cancer type, and “chimeric antigen.”

*Major target antigen for that cancer type with multiple clinical trials.

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CNS, central nervous system; EpCAM, epithelial cell adhesion molecule; FAP, fibroblast activation protein; GD2, disialoganglioside; GP3, glycoprotein 3; HCC, hepatocellular carcinoma; IL, interleukin; MDS, myelodysplastic syndrome; MIM, multiple myeloma; MUC1, mucin 1; MSLN, mesothelin; PSMA, prostate-specific membrane antigen; ROR, receptor tyrosine kinase-like orphan receptor.
inhibitors are effective in relapsed ChL, with manageable safety profiles. Clinical trials using combination studies with chemotherapy, other biologic agents, and cellular therapy, as well as use in untreated patients, are still in progress. CD19 CAR T cells have demonstrated tremendous success for the treatment of NHL. Despite these successes, several limitations remain, including broadening applicability for a patient-specific product, toxicities, antigen loss, and cost. Future directions are focusing on extending the CAR antigen repertoire for NHL to include not only CD20 and CD30 but also ROR1 (tyrosine-protein kinase receptor), BAFF (B-cell activating factor), and other surface markers, including T-cell NHL markers such as CD5 and CD7. Future clinical trials will build on the success of CD19 CAR T cells, with aims to not only evaluate other CAR T-cell products (beyond CD19) but also to reduce the cost and time necessary for manufacturing patient-specific products and decrease the incidence of severe AEs, all in an effort to improve outcomes for patients with NHL. Although these developments are exciting, the cost and accessibilities of these therapies should be considered when they are offered to patients. Referral to specialized treatment centers is recommended to provide safe and efficient treatments.

References


TREATMENT OF PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA: FROM CHEMOTHERAPY TO SMALL MOLECULES

Joe S. Mendez, MD, and Christian Grommes, MD

OVERVIEW

Primary central nervous system lymphoma (PCNSL) is a rare form of extranodal non-Hodgkin lymphoma that is typically confined to the brain, eyes, and cerebrospinal fluid (CSF) without evidence of systemic spread. PCNSL is an uncommon tumor, and only four randomized trials and one phase III trial have been completed so far, all in the first-line setting. The prognosis of patients with PCNSL has improved during the past few decades with the introduction of high-dose methotrexate (HD-MTX), which now serves as the backbone of all first-line treatment regimens. Despite recent progress, results after treatment are durable in half of patients, and therapy can be associated with late neurotoxicity. Novel insights into the pathophysiology of PCNSL have identified the B-cell receptor (BCR) pathway as a key mechanism in the pathogenesis of PCNSL. The use of novel agents targeting components of the BCR pathway, namely the Bruton tyrosine kinase (BTK) inhibitor ibrutinib, and immunomodulatory drugs (IMIDs) like lenalidomide and pomalidomide, has so far been limited to patients who have recurrent/refractory PCNSL with promising high response rates. Within the past 5 years, there has been a peak in clinical trials investigating small molecules and novel reagents in the recurrent/refractory setting, including immune checkpoint inhibitors, IMIDs, and BTK and PI3K/AKT/mTOR inhibitors.

PCNSL is a highly aggressive non-Hodgkin lymphoma confined to the central nervous system (CNS), including the brain, spine, CSF, and eyes. Unlike other primary brain tumors, it often has a favorable response to both chemotherapy and radiation therapy; however, compared with lymphomas outside the CNS, survival is usually inferior. Moreover, the prognosis for PCNSL that fails to respond to first-line therapy remains poor. Even though new chemotherapy-based therapeutic approaches have improved survival, the management of this disease still poses a challenge in neuro-oncology.

EPIDEMIOLOGY

PCNSL can develop in patients who are immunosuppressed (HIV/AIDS, organ transplantation, immunosuppressive agents) or immunocompetent. In this review, we will focus on the latter. PCNSL in the immunocompetent patient is rare and represents only 4% of all intracranial neoplasms and 4% to 6% of all extranodal lymphomas.1 Approximately 1,500 new patients are diagnosed each year in the United States. In recent years, an increasing incidence has been recognized in patients older than age 60, in whom the annual incidence rate is 0.5 per 100,000.2

The overall incidence rate of PCNSL has remained stable since the mid-1980s,3 other than a sharp spike in PCNSL incidence in the early 1990s that most likely was due to the HIV epidemic. The overall increase in PCNSL seen in the 1980s is a reflection of a growing elderly population with a longer life expectancy. The highest incidence rates are observed in patients age 60 and older, and the highest rates are in those age 70 to 79 (4.3 per 100,000 per year).3

CLINICAL PRESENTATION

Diagnosis of PCNSL requires a high level of suspicion, because clinical presentations vary according to the involved compartments. Focal neurologic deficits, which result from involvement of the parenchyma or leptomeninges, lead to prompt imaging but are only seen in 70% of patients.4 Up to 43% of individuals have behavioral or neuropsychiatric changes that are nonspecific, which can lead to a delay in medical evaluation. Signs of elevated intracranial pressure, such as headache, nausea, and vomiting, are also common (33%). Because the cortex is relatively spared, few patients (14%) present with seizures. Patients with ocular involvement may complain of blurred vision, decreased acuity, or floaters, but visual symptoms at presentation are rare (4%) despite the frequency of ocular involvement (20% to 25%).5,6 However, these symptoms are often subtle, and asymptomatic ocular involvement is common. Ocular lymphoma resembles uveitis and may be misdiagnosed if visual symptoms are not specifically sought.

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Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

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complaints are the only clinical manifestation. The classic B symptoms seen in patients with non-CNS lymphoma are uncommon in PCNSL.

DIAGNOSIS AND STAGING

Patients with symptoms concerning for PCNSL should undergo brain imaging. Contrast enhanced MRI is the modality of choice. PCNSL can appear as a solitary lesion or multifocal disease. Lesions are often periventricular and involve the deep white matter, basal ganglia, or corpus callosum. Classically, the lesions are isointense to hyperintense on T2 MRI sequencing (Fig. 1). Lesions are homogeneously enhancing with a mild amount of edema and are often associated with diffusion-weighted imaging restriction. Less frequently, the eyes (15% to 25%), CSF (7% to 42%), and—only rarely—spinal cord are involved. To assess the extent of disease, the International PCNSL Collaborative Group recommends baseline staging of the neuroaxis with an MRI brain, MRI spine (if spinal symptoms are present), and ophthalmologic and CSF evaluation. Diagnostic diagnosis requires pathologic confirmation, which often necessitates brain biopsy. The diagnostic procedure of choice to establish the diagnosis of PCNSL is a stereotactic biopsy; if ocular or CSF involvement is evident, vitrectomy or CSF cytology may be sufficient. Corticosteroids should always be deferred until tissue is obtained, except in cases of life-threatening mass effect and edema, because corticosteroids are lymphotoxic and can obscure pathology results. To detect the presence of non-CNS disease, a body PET/CT scan and bone marrow biopsy should be performed.

PROGNOSIS

To predict outcome and better stratify patients in clinical trials, two major scoring systems have been established and are widely applied: the International Extranodal Lymphoma Study Group score and the Memorial Sloan Kettering Cancer Center prognostic score. The International Extranodal Lymphoma Study Group score uses age, Eastern Cooperative Oncology Group performance score, lactate dehydrogenase level, CSF protein concentration, and deep brain involvement to determine prognosis. The presence of 0 to 1, 2 to 3, or 4 to 5 adverse risk factors correlates with 2-year survival rates of 80%, 48%, or 15%, respectively. The Memorial Sloan Kettering Cancer Center prognostic score distinguishes three groups on the basis of age and Karnofsky performance status (KPS): (1) age 50 or younger; (2) age older than 50 plus KPS of 70 or greater; and (3) age older than 50 plus KPS less than 70. These groups correlate with a median overall survival (OS) of 8.5, 3.2, and 1.1 years in the Memorial Sloan Kettering Cancer Center population and 5.2, 2.1, and 0.9 years in a validation cohort.

The median OS of patients with PCNSL in the United States (according to the Surveillance, Epidemiology, and End Results database) doubled from 12.5 months in the 1970s to 26 months in the 2010s. Unfortunately, this survival benefit was limited to patients younger than age 70. More importantly, the survival of the elderly population has not changed in 40 years and remains poor at 6 months.

Disease recurrence is commonly observed in patients with PCNSL and rarely occurs outside the CNS. Despite advances in initial treatment, up to half of patients experience relapse, and 10% to 15% have primary refractory disease. Patients with primary refractory or relapsed PCNSL have a poor prognosis and a median survival of 2 months without

PRACTICAL APPLICATIONS

- The majority of PCNSLs are DLBCLs of the nongerminatal center subtype.
- Methotrexate forms the backbone of first-line chemotherapy regimens.
- Targeted agents have not been included in first-line treatment of PCNSL.
- BCR signaling is frequently affected by mutations in PCNSL.
- Targeting of the BCR signaling axis has promising clinical activity in recurrent/refractory PCNSL.
additional treatment. Median time to relapse is 10 to 18 months, and most relapses occur within the first 2 years of initial diagnosis. However, relapsed disease has been observed more than 5 years after initial diagnosis. 

**EVOLUTION OF STANDARD THERAPY**

**First-Line Therapy**

Treatment of PCNSL has evolved during the past few decades, but no uniform consensus on the optimal treatment regimen currently exists. PCNSL has been found to be highly sensitive to chemotherapy (Fig. 2). The role of surgery has generally been restricted to stereotactic biopsy, because tumor growth is diffusely infiltrative, and no survival benefit has been obtained from subtotal or gross total resection in retrospective studies. In the early 1980s, treatment with whole brain radiotherapy (WBRT) was established for patients with newly diagnosed PCNSL, because increased relapses in regions outside the radiation port were seen with focal radiation. WBRT resulted in overall response rates (ORRs) of 90%, but OS was limited to only 12 to 18 months. To improve clinical outcome more, chemotherapy was added to WBRT in the 1980s and 1990s. Regimens used in non-CNS disease, such as cyclophosphamide, doxorubicin, vincristine, and prednisone, were ineffective, partly because of inadequate penetration of the blood-brain barrier. A breakthrough was reached with the introduction of HD-MTX in combination with WBRT, which improved median OS to 30 to 60 months and had 5-year survival rates of 30% to 0%. Although survival was prolonged, patients treated with chemotherapy developed neurotoxicity that manifested as psychomotor slowing, memory dysfunction, behavioral changes, gait ataxia, and incontinence, which all resulted in great functional decline. Patients older than age 60 are particularly affected by neurotoxicity. Moreover, the only phase III randomized study conducted in PCNSL examined whether omission of WBRT affected survival. In this study, all patients received HD-MTX with or without ifosfamide, and those whose disease achieved a complete response were randomly assigned to receive 45 Gy of WBRT or observation. Those patients whose disease failed to achieve a complete response were randomly assigned to 45 Gy of WBRT or high-dose cytarabine. The study demonstrated that patients who received WBRT had a significantly longer progression-free survival (PFS) of 18 months compared with those who did not receive WBRT (12 months), but no difference in OS was appreciated. On the basis of this data and the high risk of neurotoxicity, most clinicians eliminate WBRT as part of routine care of patients with PCNSL.

In an effort to reduce neurotoxicity, chemotherapy-only trials were conducted with single-agent HD-MTX. Polychemotherapy regimens (including rituximab, a monoclonal antibody–directed against the B-cell surface antigen CD20) demonstrated an ORR of 35% to 74% and a median OS of 25 to 50 months, which were comparable to chemoradiation trials.

Different polychemotherapy regimens that consisted of induction and consolidation phases have been used with comparable response rates and OS (Table 1). Currently, HD-MTX (at doses greater than 3 g/m² every 2 weeks) and rituximab should be part of any first-line induction treatment. Regimens currently used are as follows: rituximab/methotrexate/vincristine/procarbazine, rituximab/methotrexate/temozolomide, rituximab/methotrexate/thiotepa/cytarabine, and rituximab/methotrexate/teniposide/carmustine/prednisone. Because no comparison studies have been conducted, the regimen used is dependent on geographic region and physician preference. The only comparison study evaluated HD-MTX with temozolomide compared with HD-MTX, vincristine, and procarbazine in an elderly population (age ≥ 60) in a multicenter phase II trial. Toxicity profiles were similar between the groups. The ORR was 82% in the HD-MTX, vincristine, and procarbazine group and was 71% in the HD-MTX with temozolomide group; the median OS times were 31 and 14 months, respectively. Although these trends were not statistically significant, the results favored the HD-MTX, vincristine, and procarbazine regimen. One major obstacle for patients with PCNSL...
receiving MTX is the drug’s nephrotoxicity. MTX can precipitate in renal tubules, particularly with acidic urine, volume depletion, and sustained high MTX plasma levels. Therefore, most patients with PCNSL are admitted to the hospital for MTX treatment, placing a higher burden on patients and their families compared with the outpatient treatment regimen.

For consolidation, the following treatments have been used and are all valid options: radiation therapy (23.4 or 45 Gy), conventional high-dose chemotherapy (cytarabine or etoposide/cytarabine),40 myeloablative chemotherapy with autologous stem-cell rescue (in younger patients and patients with adequate organ function), or observation. Observation typically is reserved for elderly patients or those unable to tolerate additional treatment. In addition, age and response to induction therapy guide the choice of consolidation strategy. Ongoing trials that randomly assign patients to different consolidation treatments will, we hope, shed more light on the optimal consolidation regimen.

**Salvage Therapy**

Numerous small retrospective studies have been conducted (Table 2). WBRT and HD-MTX rechallenge seem effective. Rechallenge in patients with methotrexate led to an ORR of 85% to 91% and a median OS of 41 to 62 months. WBRT was associated with an ORR of 74% to 79% and a median OS of 10 to 16 months and might be considered in patients who have not received it as a part of initial therapy. The efficacy of HD-MTX rechallenge or WBRT has not been evaluated in prospective studies so far. However, HD-MTX rechallenge can be considered as the most frequently used treatment regimen in patients with recurrent PCNSL, especially when there is a long period of remission after initial HD-MTX therapy and the patient has experienced a disease response to HD-MTX before.

Prospective trials that use single agents, such as pemetrexed,68 topotecan,64 temozolomide,65 or rituximab,87,89 have demonstrated modest ORRs of 31% to 55% and limited median PFS times of 1.6 to 5.7 months (Table 2). The optimal salvage regimen for patients with recurrent or refractory PCNSL has not been established. As with the first-line regimens, age, performance status, previous therapies, and duration of prior response are factors that influence the choice of salvage treatment until data from randomized clinical trials identify the optimal treatment regimen for patients with recurrent disease.

No randomized trials have been conducted so far in this patient population. This gap occurs in part because of (1) limited insights into the pathophysiology of this disease to point to specific drug targets and (2) the heterogeneous sites of recurrence (brain, CSF, eyes, or combination thereof), number of recurrences, and age at recurrence.

**NOVEL INSIGHTS**

Most PCNSLs (90%) are diffuse large B-cell lymphoma (DLBCL) and, rarely, Burkitt, low-grade, or T-cell lymphoma.72 Pathologic review of PCNSL samples reveals highly proliferative tumor cells in a typical angiocentric growth pattern that diffusely infiltrate the CNS (Fig. 3A). Gene expression profiling has identified three molecular subgroups of non-CNS DLBCL: the germinal center B-cell–like, activated B-cell–like/nongerminall center, and type-3 subgroups.73 Staining of PCNSL biopsies with antibodies that distinguish these DLBCL subgroups6 (CD10, BCL6, MUM-1/IRF4; Fig. 3B–D) showed that the vast majority (> 80%) of PCNSLs were the nongerminall center subtype.71,75 Outside the CNS, this DLBCL subgroup is associated with inferior outcomes and mutations in the BCR pathway.76

In PCNSL cohorts71,77-83 the BCR signaling axis with its downstream target, nuclear factor-kappa B (NFκB), is affected by frequent recurrent mutations, mainly in MYD88 and CD79B and less frequently in CARD11 and TNFAIP3 (Fig. 4A). MYD88 and CD79B mutations are enriched in activated B-cell–like/nongerminall center PCNSLs and are more often observed in PCNSLs than in activated B-cell–like DLBCL outside the CNS.84 MYD88 and CD79B mutations are also frequently found in lymphoma in other immune-privileged sites, like the testis.85 Interestingly, in PCNSLs MYD88 and/or CD79B mutations also are found in germinal center B-cell–like samples.71,87 The majority of these mutations are missense mutations with hotspot mutations in MYD88 (L265P) and CD79B (Y196). Immunohistochemical staining of MUM1, a transcriptional target of NFκB, is positive in 70% to 95%71,72,88 of PCNSLs, which suggests that the BCR signaling axis is an important driving event in PCNSL. The BCR signaling pathway may be targeted at different signaling nodules (Fig. 4B): (1) upstream: spleen tyrosine kinase, phosphatidylinositol-4,5-bisphosphate 3-kinase, BTK inhibitors, and interleukin-1 receptor–associated kinase inhibitors; and (2) downstream: the IMID thalidomide and its analogs lenalidomide and pomalidomide, which inhibit IRF4, mucosa-associated lymphoid tissue lymphoma translocation protein 1 inhibitors, or proteasome inhibitors like bortezomib.

In cohorts of up to 22 patients, copy number alterations, mainly loss of 6q, gain of 12q, gain of 18q, gain of 19q, and gain of 22q,89-93 have been observed. TNFAIP3, a regulator of NFκB signaling, is located on chromosome 6q, another indicator that BCR signaling is frequently affected by genomic alterations. Recently, copy number gains at chromosome 9p24.1, the PD-L1/PD-L2 locus, have been described, which suggests that immune evasion might play a role in PCNSL. In addition, aberrant somatic hypermutation, a prominent feature of systemic DLBCL, also has been identified in PCNSL77,95,96 and is characterized by mutations that are (1) within 20,000 base pairs of the transcription start site, (2) within a WGYR motif, (3) have transition compared with transversion mutations, and (4) have C/T versus A/G mutations. Aberrant somatic hypermutation often affects PIM1, BTG2, PRDM1, TOX, and IRF4 in PCNSL.71,87 Amplification of chromosome 9p24.1 and frequent aberrant somatic hypermutation might increase susceptibility to immune checkpoint inhibitors like nivolumab or pembrolizumab.
### TABLE 1. Prospective Up-Front Treatment Trials in Primary Central Nervous System Lymphoma

<table>
<thead>
<tr>
<th>Study by Treatment Type</th>
<th>Agent</th>
<th>No. of Patients</th>
<th>ORR (PR + CR), No./Total No. (%)</th>
<th>Median OS, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson et al24</td>
<td>Radiotherapy 40 Gy + 20-Gy boost</td>
<td>41</td>
<td>21/26 (80)</td>
<td>12.2</td>
</tr>
<tr>
<td><strong>Chemoradiation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schultz et al27</td>
<td>CHOP + radiotherapy 41.4 Gy + 18-Gy boost</td>
<td>52</td>
<td>10/52 (19)</td>
<td>16.1</td>
</tr>
<tr>
<td>O’Neill et al26</td>
<td>CHOP + radiotherapy 50.4 Gy + cytarabine</td>
<td>55</td>
<td>32/53 (60)</td>
<td>9.7</td>
</tr>
<tr>
<td>Mead et al28</td>
<td>Radiotherapy 40 Gy + 14-Gy boost ± CHOP</td>
<td>53</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>DeAngelis et al29</td>
<td>Methotrexate 1 g/m² + radiotherapy 40 Gy + 14-Gy boost + cytarabine 3 g/m²</td>
<td>31</td>
<td>27/31 (87)</td>
<td>42.5</td>
</tr>
<tr>
<td>Glass et al20</td>
<td>Methotrexate 3.5 g/m² + radiotherapy 30–40 Gy</td>
<td>25</td>
<td>23/25 (90)</td>
<td>33</td>
</tr>
<tr>
<td>O’Brien et al21</td>
<td>Methotrexate 1 g/m² + radiotherapy 45 Gy + 5.4-Gy boost</td>
<td>46</td>
<td>44/46 (96)</td>
<td>33</td>
</tr>
<tr>
<td>Abrey et al22</td>
<td>Methotrexate 3.5 g/m² + prednisone 100 mg + vincristine 1.4 mg/m² + cytarabine 3 g/m² + IT methotrexate + IT cytarabine + radiotherapy 45 Gy</td>
<td>52</td>
<td>49/52 (94)</td>
<td>60</td>
</tr>
<tr>
<td>Ferreri et al23</td>
<td>Methotrexate 3 g/m² + prednisone 100 mg + vincristine 1.4 mg/m² + cytarabine 3 g/m² + radiotherapy 45 Gy</td>
<td>13</td>
<td>12/13 (92)</td>
<td>≥ 25</td>
</tr>
<tr>
<td>DeAngelis et al29</td>
<td>Methotrexate 2.5 g/m² + vincristine 1.4 mg/m² + prednisone 100 mg + cytarabine 3 g/m² + IT methotrexate + radiotherapy 45 Gy</td>
<td>102 (98 treated)</td>
<td>47/50 (94)</td>
<td>37</td>
</tr>
<tr>
<td>Poortmans et al25</td>
<td>Methotrexate 3 g/m² + teniposide 100 mg/m² + carmustine 100 mg/m² + methylprednisolone 60 mg + IT methotrexate + IT cytarabine + radiotherapy 40 Gy</td>
<td>52</td>
<td>42/52 (81)</td>
<td>46</td>
</tr>
<tr>
<td>Ferreri et al26</td>
<td>Methotrexate 3.5 g/m² + cytarabine 2 g/m² + radiotherapy 45 Gy</td>
<td>79</td>
<td>27/39 (69) vs. 16/40 (40)</td>
<td>NR</td>
</tr>
<tr>
<td>Thiel et al27</td>
<td>Methotrexate 3 g/m² + ifosfamide ± radiotherapy 45 Gy</td>
<td>526 (all)/318 (PPP)</td>
<td>283/526 (53)</td>
<td>32.4 vs. 37.1</td>
</tr>
<tr>
<td>Morris et al28</td>
<td>Rituximab 500 mg/m² + methotrexate 3.5 g/m² + vincristine 1.4 mg/m² + prednisone 100 mg + radiotherapy 23.4 Gy</td>
<td>52</td>
<td>41/52 (78)</td>
<td>NR</td>
</tr>
<tr>
<td>Glass et al29</td>
<td>Rituximab 375 mg/m² + methotrexate 3.5 g/m² + temozolomide 100 mg/m² + radiotherapy 36 Gy</td>
<td>66</td>
<td>30/35 (86)</td>
<td>90</td>
</tr>
<tr>
<td><strong>Chemotherapy only</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herlinger et al37</td>
<td>Methotrexate 8 g/m²</td>
<td>37</td>
<td>13/37 (35)</td>
<td>25</td>
</tr>
<tr>
<td>Batchelor et al39</td>
<td>Methotrexate 8 g/m²</td>
<td>25</td>
<td>17/23 (74)</td>
<td>22.8+</td>
</tr>
<tr>
<td>Pels et al38</td>
<td>Methotrexate 5 g/m² + cytarabine 3 g/m² + vincristine 2 mg/m² + ifosfamide 800g/m² + dexamethasone 10 mg + cyclophosphamide 200 mg/m² + IT methotrexate, IT cytarabine, and IT prednisone</td>
<td>65</td>
<td>43/61 (71)</td>
<td>50</td>
</tr>
<tr>
<td>Rubinstein et al40</td>
<td>Rituximab 375 mg/m² + methotrexate 8 g/m² + temozolomide 150 mg/m² + cytarabine 2 g/m² vs. etoposide 40 mg/m²</td>
<td>44</td>
<td>34/47 (72)</td>
<td>NR</td>
</tr>
<tr>
<td>Ferreri et al41</td>
<td>Methotrexate 3.5 g/m² + cytarabine 2 g/m²; ± rituximab 375 mg/m² ± thiotepa 30 mg/m²</td>
<td>227</td>
<td>40/75 (53); 51/69 (73); 65/75 (86)</td>
<td>12/30/NR</td>
</tr>
<tr>
<td>Omuro et al42</td>
<td>Methotrexate 3.5 g/m² + vincristine 1.4 mg/m² + prednisone 100 mg + cytarabine 3 g/m² vs. methotrexate 3.5 g/m² + temozolomide 150 mg/m²</td>
<td>95</td>
<td>37/45 (82) vs. 34/42 (74)</td>
<td>31 vs. 14</td>
</tr>
<tr>
<td><strong>Chemotherapy only with SCT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abrey et al43</td>
<td>Methotrexate 3.5 g/m² + cytarabine 3 g/m²; BEAM</td>
<td>28 (14 underwent transplantation)</td>
<td>Induction: 16/24 (57), SCT 11/14 (77)</td>
<td>NR</td>
</tr>
<tr>
<td>Colombat et al44</td>
<td>Methotrexate 3 g/m² + carmustine 100 mg/m² + etoposide 100 mg/m² + prednisone 60 mg; BEAM + radiotherapy 30 Gy</td>
<td>25 (17 underwent transplantation)</td>
<td>Induction: 21/25 (84), SCT 16/16 (100)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Continued
Frequent inactivation of \textit{CDKN2A} through mutations or deletion has been described in PCNSL \cite{81,82,97} and could be exploited therapeutically through cyclin-dependent kinase inhibitors. Moreover, venetoclax, a BCL2 inhibitor, might present an additional small molecule with activity in PCNSL; 56% to 93% of PCNSL tumors express BCL2. \cite{72,88}

**SMALL MOLECULES APPLIED IN PCNSL**

On the basis of these new, exciting insights in PCNSL, small molecules have found their way in clinical trials for recurrent/refractory PCNSL. The first targeted agent reported was the mTOR inhibitor temsirolimus in a German multicenter phase II trial. \cite{98} Treatment was associated with an ORR of

<table>
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<tr>
<th>TABLE 1. Prospective Up-Front Treatment Trials in Primary Central Nervous System Lymphoma (Cont’d)</th>
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<tbody>
<tr>
<td><strong>Study by Treatment Type</strong></td>
</tr>
<tr>
<td><strong>Omuro et al\textsuperscript{82}</strong></td>
</tr>
<tr>
<td><strong>Illerhaus et al\textsuperscript{88}</strong></td>
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</table>

*Abbreviations: BEAM, carmustine, etoposide, cytarabine, and melphalan; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response; IT, intrathecal; NR, not reported; ORR, overall response rate; OS, overall survival; PP, per-protocol population; PR, partial response; SCT, stem-cell transplantation.*

<table>
<thead>
<tr>
<th>TABLE 2. Salvage Regimens in Primary Central Nervous System Lymphoma</th>
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<tr>
<td><strong>Study by Design</strong></td>
</tr>
<tr>
<td><strong>Retrospective</strong></td>
</tr>
<tr>
<td>Herrlinger et al\textsuperscript{54}</td>
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<tr>
<td>Arellano-Rodrigo et al\textsuperscript{55}</td>
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<tr>
<td>Wong et al\textsuperscript{56}</td>
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<tr>
<td>Enting et al\textsuperscript{57}</td>
</tr>
<tr>
<td>Plotkin et al\textsuperscript{58}</td>
</tr>
<tr>
<td>Nguyen et al\textsuperscript{59}</td>
</tr>
<tr>
<td>Hottinger et al\textsuperscript{60}</td>
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<tr>
<td>Makino et al\textsuperscript{61}</td>
</tr>
<tr>
<td>Wong et al\textsuperscript{62}</td>
</tr>
<tr>
<td>Zhang et al\textsuperscript{63}</td>
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<tr>
<td>Pentsova et al\textsuperscript{64}</td>
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<tr>
<td>Chamberlain\textsuperscript{65}</td>
</tr>
<tr>
<td>Houillier et al\textsuperscript{66}</td>
</tr>
<tr>
<td>Chamberlain\textsuperscript{67}</td>
</tr>
<tr>
<td><strong>Prospective</strong></td>
</tr>
<tr>
<td>Fischer et al\textsuperscript{68}</td>
</tr>
<tr>
<td>Reni et al\textsuperscript{69}</td>
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<tr>
<td>Soussain et al\textsuperscript{70}</td>
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<tr>
<td>Batchelor et al\textsuperscript{71}</td>
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<td>Raizer et al\textsuperscript{72}</td>
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<td>Rubenstein et al\textsuperscript{73}</td>
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<td>Nayak et al\textsuperscript{74}</td>
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<tr>
<td>Korfel et al\textsuperscript{75}</td>
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<tr>
<td>Grommes et al\textsuperscript{76}</td>
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</table>

*Abbreviations: CR, complete response; CYVE, cytarabine/etoposide; IT, intrathecal; NR, not reported; ORR, overall response rate; OS, overall survival; PCNSL, primary central nervous system lymphoma; PFS, progression-free survival; PR, partial response; SCT, stem-cell transplantation; WBRT, whole-brain radiation.*
54%, but median PFS was only 2.1 months. Another trial targeting the PI3K/mTOR axis used the pan-PI3K inhibitor buparlisib and showed an ORR of 25%. The study included blood and CSF pharmacokinetic assessments. Although plasma concentrations were similar to reported data, the CSF drug concentrations were less than the 50% inhibitory concentration required to induce cell death in vitro, which potentially led to a lack of clinical response. The concept of PI3K inhibition is still under investigation in a multicenter phase I/II trial that is testing use of the dual pan–PI3K/mTOR inhibitor PQR309 (NCT02669511).

Targeting the BCR pathway at the central signaling nodule, BTK, has produced more promising results. Two studies used the BTK inhibitor, ibrutinib, at 560 and 840 mg daily. In the 560-mg trial (NCT02542514), 52 patients with recurrent PCNSL or ocular lymphoma were enrolled in a French study, and the ORR was 50% after the first two cycles of ibrutinib. In the 840-mg trial (NCT02315326), 20 patients with recurrent PCNSL and secondary CNS lymphoma achieved an ORR of 75% (77% in PCNSL; 13 patients) and 71% in secondary CNS lymphoma; 7 patients), and the PCNSL group had a median PFS of 4.6 months.

FIGURE 3. Histologic Features of Primary Central Nervous System Lymphoma

(A) Hematoxylin and eosin staining of a PCNSL biopsy sample demonstrating the angiocentric growth pattern of PCNSL. (B–D) Diffuse large B-cell lymphoma subgroup determination using three immunohistochemical markers (CD10, BCL-6, MUM-1) according to the Hans algorithm. The majority of PCNSLs are of the nongerminai center/activated B-cell subtype and display a similar staining pattern: CD10 negative (B), BCL-6 positive (C), and MUM-1 positive (D).

Abbreviation: PCNSL, primary central nervous system lymphoma.

FIGURE 4. Genomic Landscape of Primary Central Nervous System Lymphoma

(A) The graph shows the frequency of mutated genes in different PCNSL sequencing projects. This analysis only includes single nucleotide variants and no copy number alterations. The y axis shows the percentage of affected patient cases in each study (range, 9 to 177 patients). Members of the BCR signaling axis (asterisks) are frequently affected. (B) Cartoon of the BCR/nuclear factor-kappa B signaling axis. Genes harboring mutations in PCNSL are highlighted (asterisks). Signaling nodes that can be inhibited with targeted agents are highlighted.

Abbreviations: PCNSL, primary central nervous system lymphoma; BCR, B-cell receptor.
Last, a study at the National Institutes of Health showed that 15 (83%) of 18 patients with PCNSL experienced a radiographic response after 2 weeks of ibrutinib treatment. The results of this study are more difficult to interpret, because newly diagnosed patients with PCNSL (5 of 18) were included, multiple other drugs were added after the initial 2-week ibrutinib monotherapy window, and a much higher frequency of infectious complications occurred (e.g., 39% Aspergillus infection rate) compared with single-agent ibrutinib studies (e.g., 2 [3.8%] of 52 patients with this infection in the 560-mg study and 1 [5%] of 20 patients in the 840-mg study). The clinical efficacy of single-agent ibrutinib is remarkable: response rates are high, and PFS is longer than that observed with conventional chemotherapy in this patient population. Moreover, the response observed in the CNS is substantially higher than in patients with non-CNS DLBCL who are treated with ibrutinib (e.g., 25% ORR with single-agent ibrutinib and a PFS of only 2 months), which is not often seen in neuro-oncology. Even patients without genomic alteration in the BCR pathway experienced a response to ibrutinib. The mechanisms of ibrutinib resistance that limit PFS must be investigated more.

The IMIDs lenalidomide and pomalidomide have been used in PCNSL alone or in combination with rituximab. IMIDs not only inhibit NF-κB activity but also inhibit the PI3K/AKT pathway, so they represent promising agents. Indeed, a phase I/II trial of single-agent pomalidomide in recurrent/refractory PCNSL demonstrated an ORR of 50% at the maximally tolerated dose. Similarly, ORRs of 62% and 67% were seen with the combination of lenalidomide and rituximab. Another promising approach might be the use of immune checkpoint inhibitors. Nayak et al reported a 100% response rate in a small retrospective study of five patients who experienced durable responses. This observation sparked a multicenter trial to investigate single-agent nivolumab in PCNSL and testicular lymphoma (NCT02857426). In parallel, a single-institution trial with pembrolizumab (NCT02779101) is ongoing to investigate the concept of PD-1 blockade in PCNSL.

FUTURE DIRECTIONS

Although targeting molecular abnormalities identified in archival PCNSL tissue samples has made a great impact in the recurrent/refractory setting and has had impressive response rates, PFS is still limited, and patients are far from a cure. Moving forward, combinations of different targeted inhibitors for better complete pathway inhibition and inhibition of parallel pathways must be evaluated. In addition, targeted inhibitors must be combined with conventional and active agents used in the first-line setting (e.g., HD-MTX, rituximab). The TEDDI-R101 regimen was the first approach to combine a novel agent with chemotherapy in PCNSL; it provided an impressive clinical response but also unexpected devastating adverse events. The combination of ibrutinib with HD-MTX, as well as ibrutinib with HD-MTX and rituximab, has been tested and found to be safe; the aim is to move combination therapies with targeted agents to the first-line setting. It will be interesting to see how, and if, small molecules will be combined with new exciting treatment approaches, such as chimeric antigen receptor T cells.

CONCLUSION

Great progress has been made in the treatment of PCNSL during the past few decades. Targeted agents have found their way into the recurrent/refractory setting and, because of promising clinical responses, additional agents will follow. Over the next years, we will likely see small molecules being integrated into first-line treatments to reduce the number of patients with refractory disease, to prolong remission, and to increase treatment options for patients with recurrent disease that has a particularly poor outcome. Moreover, small molecules might help improve outcomes in the elderly population by reducing treatment-associated comorbidities seen more often with conventional therapies.

ACKNOWLEDGMENT

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References


Large granular lymphocyte (LGL) leukemia has been recognized in the World Health Organization classifications among mature T cell and natural killer cell neoplasms and is divided into three categories. Chronic T cell leukemia and natural killer cell lymphocytosis can be considered as a similar spectrum of an indolent disease characterized by cytopenias and autoimmune conditions. The last category, aggressive natural killer cell LGL leukemia is very rare, related to Epstein-Barr virus, and seen mainly in young Asian people. Clonal LGL expansion arises from chronic antigenic stimulation sustained by interleukin-15 and platelet-derived growth factor cytokine signal. Those leukemic cells are resistant to apoptosis, mainly because of constitutive activation of survival pathways including Jak/Stat, MapK, Pi3k-Akt, RasRaf-1, MEK1/ERK, sphingolipid, and NFkB. Stat3 constitutive activation is the hallmark of this lymphoproliferative disorder. Socs3 is downregulated, but no mutation could be found to explain this status. However, several somatic mutations, including Stat3, Stat5b, and tumor necrosis factor alpha–induced protein 3, have been demonstrated recently in LGL leukemia; they are identified in half of patients and cannot explain LGL leukemogenesis. Recurrent infections as a result of chronic neutropenia, anemia, and autoimmune disorders are the main complications related to LGL leukemia. Despite an indolent presentation, 10% of patients die, mainly because of infectious complications. Current treatments are based on immunosuppressive therapies. A better mechanistic understanding of LGL leukemia will allow future consideration of a personalized therapeutic approach perhaps based on Jak/Stat inhibitors, which may offer better results than current immunosuppressive therapy.
remain asymptomatic at the time of diagnosis. Initial presentation is dominated by recurrent infections related to chronic neutropenia. A quarter of patients harbor splenomegaly, although hepatomegaly or lymphadenopathy is rarely observed. As LGL leukemia is an indolent disease, B symptoms are rare, with fatigue and B symptoms observed in only 20% to 30% of the cases.

Less than half of patients present with lymphocyte counts of $4 \times 10^9/L$ to $10 \times 10^9/L$. The two biggest series reported an average LGL count of about $1.7 \times 10^9/L$. A lower LGL count ($0.5 \times 10^9/L$ to $1 \times 10^9/L$) may be observed in 7% to 36% of cases. Fifty percent of patients are neutropenic, and about 20% of them have severe neutropenia. Recurrent oral aphthous ulcers are frequently observed, although some neutropenic patients remained asymptomatic. Infections secondary to chronic neutropenia involve primarily skin, oropharynx, and the perirectal area and affect 15% to 39% of patients. Severe septic complications may occur and represent the primary cause of related death, affecting about 5% to 10% of patients. Transfusion-dependent anemia affects between 6% and 22% of patients according to series, and pure red cell aplasia occurs in 8% to 19% of cases. Thrombocytopenia is less severe and described in fewer than 20% of cases.

Positivity of rheumatoid factor (40%–60%), antinuclear antibodies (40%), antineutrophil antibodies (20%–60%), or direct Coombs underlines the immune context of this lymphoproliferative disorder.9 Indeed, LGL leukemia is commonly associated with autoimmune diseases (15%–40% according to the series).10 Rheumatoid arthritis is present in about 15% of the cases. Autoimmune cytopenias are reported among 5% to 10% of patients. Systemic lupus erythematosus, Sjögren’s syndrome, autoimmune thyroid disorders, coagulopathy, and inclusion body myositis have occasionally been reported. Vasculitis with cryoglobulinemia was also reported. Moreover, cases of pulmonary artery hypertension considered as a vasculopathy with endothelial dysfunction were reported to be associated with LGL leukemia. LGL leukemia–associated diseases are listed in Table 2.

### TABLE 1. Clinical and Biologic Presentation: Data From the Two Largest Retrospective Series

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Bareau et al7</th>
<th>Sanikommu et al8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (y)</td>
<td>59</td>
<td>63</td>
</tr>
<tr>
<td>Sex Ratio (male/female)</td>
<td>104/124</td>
<td>110/94</td>
</tr>
<tr>
<td>T-LGL (%)</td>
<td>201 (87)</td>
<td>183 (90)</td>
</tr>
<tr>
<td>NK-LGL (%)</td>
<td>28 (13)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Symptomatic (%)</td>
<td>186 (81)</td>
<td>118 (53)</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>55 (24)</td>
<td>49 (24)</td>
</tr>
<tr>
<td>Median LGL G/L</td>
<td>1.71</td>
<td>1.74 (0.8–3.3)</td>
</tr>
<tr>
<td>ANC &lt; 1.5 G/L (%)</td>
<td>135 (59)</td>
<td>93 (46)</td>
</tr>
<tr>
<td>ANC &lt; 0.5 G/L (%)</td>
<td>56 (24)</td>
<td>36 (17)</td>
</tr>
<tr>
<td>Anemia (&lt; 11 g/dL; %)</td>
<td>56 (24)</td>
<td>79 (40)</td>
</tr>
<tr>
<td>Hb &lt; 8 g/dL (%)</td>
<td>15 (6)</td>
<td>45 (22)</td>
</tr>
<tr>
<td>Thrombocytopenia (%)</td>
<td>40 (17)</td>
<td>59 (30)</td>
</tr>
<tr>
<td>MGUS (%)</td>
<td>13/124 (10)</td>
<td>41 (20)</td>
</tr>
</tbody>
</table>

### TABLE 2. Diseases Associated With LGL Leukemia

<table>
<thead>
<tr>
<th>Associated Disease</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune disease</td>
<td>15%–40%</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>11%–36%</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>3%</td>
</tr>
<tr>
<td>Chronic inflammatory bowel disease</td>
<td>4%</td>
</tr>
<tr>
<td>Gougerot-Sjögren’s syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Rare</td>
</tr>
<tr>
<td>Rzizomelic pseudopolyarthritis</td>
<td>Rare</td>
</tr>
<tr>
<td>Poly/myonevritis</td>
<td>Rare</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>Rare</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Rare</td>
</tr>
<tr>
<td>Autoimmune cytopenia</td>
<td>5%–10%</td>
</tr>
<tr>
<td>Pure red cell aplasia</td>
<td>5%</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>3%</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Rare</td>
</tr>
<tr>
<td>Evans’ syndrome</td>
<td>Rare</td>
</tr>
<tr>
<td>Solid or hematopoietic neoplasms</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Solid neoplasms</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td>B-cell lymphoid neoplasms</td>
<td>5%–7%</td>
</tr>
<tr>
<td>Myelodysplasia</td>
<td>&lt; 4%</td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>Rare</td>
</tr>
<tr>
<td>Chronic lymphoid leukemia</td>
<td>Rare</td>
</tr>
<tr>
<td>Viral infection (HIV, HCV, CMV, EBV)</td>
<td>Rare</td>
</tr>
<tr>
<td>Post-transplantation</td>
<td>Rare</td>
</tr>
<tr>
<td>Pulmonary arterial hypertension</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Abbreviations: ANC, absolute neutrophil count; Hb, hemoglobin; LGL, large granular lymphocyte; MGUS, monoclonal gammopathy of undetermined significance; NK, natural killer.
Serum protein electrophoresis usually shows polyclonal hypergammaglobulinemia as a result of increased immunoglobulin G and/or immunoglobulin A subclasses. Hypogammaglobulinemia is seen in 5% to 10% of patients. Defects in downregulation of immunoglobulin secretion in LGL leukemia could partly explain the development of autoantibodies and clonal B-cell malignancies observed in this disease, monoclonal gammapathy of undetermined significance being the most frequent (10%–20%). Chronic lymphoid leukemia, follicular lymphoma, and mantle cell lymphoma are also reported. Finally, solid cancers are also associated with LGL leukemia.

HOW IS LGL LEUKEMIA DIAGNOSED?
A definite diagnosis of LGL leukemia requires evidence of a chronic expanded clonal T- or NK-cell LGL population associated with an appropriate clinical context. It is based on (1) cytology, (2) immunophenotype analysis, and (3) evidence of monoclonality.

Cytology: What Do LGLs Look Like?
Large granular lymphocyte are cytotoxic cells defined as: large size (15–18 μm), an abundant cytoplasm containing typical azurophilic granules, and a reniform or round nucleus with mature chromatin (Fig. 1). In physiologic conditions, such cells represent 5% to 10% of total lymphocytes, do not exceed 0.25 G/L, and are mainly NK type. They contain cytotoxic equipment in their granulations (perforin, granzyme) and express apoptosis signal through their death receptor (Fas and TRAIL).

The first step of diagnosis is based on the identification of increased numbers of circulating LGLs. Historically, the threshold of 2 × 10^9/L was mandatory. However, numerous patients present lower clonal expansion of LGLs, typically associated with cytopenias or autoimmune conditions. A threshold of 0.5 × 10^9/L is now generally accepted. As mentioned above, only 40% to 50% of patients presents with hyperlymphocytosis at diagnosis. Clinicians and cytologists should pay attention to blood smear in case of compatible clinical presentation and LGL excess. No visual distinction can be made between a clonal LGL cell and its normal counterpart.

Immunophenotypic Analysis of LGL Leukemia
LGL leukemia is typically characterized by a post-thymic mature effector memory cell phenotype, the T-LGL subtype being predominant. Briefly, T-LGL presents CD3^+^, CD8^+, and CD57^+^ expression, and NK-LGL express CD3^−^, CD8^+^, CD16^+,^ and CD56^+^ (Fig. 2).

Typical LGL leukemic cells harbor a T CD3^+^ phenotype with an αβ^+^ T-cell receptor (TCR), CD4^−^, CD5^dim^, and CD8^+. They express cytotoxic NK cell markers including CD16 (80% of cases) and CD57 (100% of cases) and NK receptors, namely, killer immunoglobulin–like receptor and CD94/NKG2. The terminal effector memory phenotype is established on CD62L^dim^, CD45RA^−^, CD122^+, CD27^+,^ and CD28^−^ expression. CD122 corresponds to the common chain of interleukin (IL)–2 and IL-15 receptors. CD3^+/CD56^+^ T-LGL leukemias may have a more aggressive behavior associated with Stat5b mutations.13,14 A rare subset of LGL leukemia is CD4^+^ with or without coexpression of CD8, and such patients remain mostly asymptomatic. This clonal LGL proliferation seems to be driven by cytomegalovirus15-17 and associated with STAT5b mutation.18 A few cases are TCRγδ^−^, CD3^+, CD4^+, CD8^+, CD16^+/−^, and CD57^+^ phenotype and harbor very similar clinicalologic behavior as their TCRαβ counterpart.19,20

NK-LGL leukemia is characterized by the following phenotype: CD2^+/sCD3^−^/CD3ε^−^/TCRab^−^/CD4^−^/CD8^−^/CD16^+^/CD56^−^.21

Monoclonality Assessment
Diagnosis is confirmed by the detection of clonality, making it possible to distinguish reactive LGL proliferation from real LGL leukemic proliferation.

T-LGL can easily be tested for clonality on the basis of TCR rearrangement analysis. TCR γ-polymerase chain reaction analyze is routinely used. The γ chain is the first one
rearranged in T αβ and γδ lymphocytes. The variable part of CDR3 is amplified using PCR, and its size distribution is then analyzed. In case of monoclonal proliferation, the size distribution is not homogenous. Deep sequencing of TCR has demonstrated a restricted diversity of the TCR repertoire. Moreover, it provides a more quantitative assessment of clonal size, potentially useful for monitoring therapy response and evaluating minimal residual disease. Vβ TCR gene repertoire analysis can also be studied using flow cytometry. The current Vb monoclonal antibody panel covers 75% of the Vb spectrum, with a high correlation between Vb flow cytometry and TCRg–polymerase chain reaction results.

It is difficult to assess the clonality of NK-LGL, because these cells do not express TCR. Restricted expression of activating isoforms of killer immunoglobulin–like receptor has been used as a surrogate marker for monoclonal expansion.

When a diagnosis cannot easily be made in the case of pancytopenia, low LGL count, or absence of proven clonality, histologic bone marrow analysis with immunohistochemistry is mandatory. The majority of patients present with medullary infiltration composed of individual or small clusters of LGLs localized primarily in sinusoids. They are difficult to identify because they mimic granulocytic or monocytic precursors, and immunohistochemistry is needed. Clusters of eight CD81+/Tia-1 cells or six granzyme B1+ lymphocytes are considered as characteristic histopathologic findings of LGL leukemia (Fig. 3).

**Differential Diagnosis**

**Reactive LGL proliferation.** Many conditions can lead to the development of reactive LGL proliferation, including splenectomy, solid organ or bone marrow graft, viral infections (human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus), solid tumor, and non-Hodgkin lymphoma. LGL proliferations are typically poly- or oligoclonal, last only several months, and are not responsible for cytopenias.
In difficult cases, bone marrow biopsy could help because in reactive LGL proliferation, bone marrow infiltration is absent.9

**Bone marrow failure syndromes.** Bone marrow failure syndromes (aplastic anemia, paroxysmal nocturnal hemoglobinuria, and myelodysplastic syndrome [MDS]) are occasionally associated with LGL leukemia.33 STAT3 mutation was found in few patients with aplastic anemia and MDS with concomitant LGL leukemia, suggesting similar pathogenesis. In this series, STAT-3-mutated patients with aplastic anemia were more sensitive to immunosuppressive therapies, and STAT-3-mutated patients with MDS harbored a lower degree of bone marrow cellularity. Efficacy of immunosuppressive treatments directed against T lymphocyte–mediated immune response is a strong argument for a common role of autoreactive T cells in all of these diseases.33 Moreover, concurrent STAT3, DNMT3A, and TET2 mutations were found in a patient with T-LGL without MDS morphologic abnormalities, and those mutations were restricted to CD3+ T cells. The two latter mutations are recurrent mutations usually found in MDS.34

A recent study revealed several cases of unexplained cytopenia in which STAT3 mutation status could after all correct the diagnosis. Those cases were classified as MDS without typical bone marrow dysplasia nor MDS typical mutation using next-generation sequencing analysis. This review suggests that it could be useful to add Stat3 SH2 domain to the myeloid next-generation sequencing panel.35

**PATHOGENESIS**

The terminal effector memory phenotype of LGL leukemic cells suggests an initial chronic immune stimulation. Chronic viral infection and more precisely chronic human T-cell lymphotropic virus infection have been suspected. IL-15 pro

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**FIGURE 3. Bone Marrow Features in a Case of T-LGL Leukemia**

Abbreviations: LGL, large granular lymphocyte.
inflammatory cytokine and platelet-derived growth factor play a crucial role in LGL leukemia expansion by promoting NK-cell or leukemic LGL survival.

The hallmark of LGL proliferation is the constitutive activation of Stat3, initially described by Epling-Burnette et al.\(^{27}\) in 2001. This activated form of Stat3 translocates into nucleus and activates pro-survival genes such as Bcl2-family protein or Mcl-1 (myeloid cell leukemia–1).\(^{38}\) This activation is explained by common somatic gain-of-function Stat3 mutations in 28% to 75% of patients with T-LGL and 30% to 48% of NK-LGL lymphocytosis.\(^{37}\) Those differences may be related to sequencing technique and patient selection. Mutations driving the dimerization and activation of Stat3 protein are located primarily in exons 20 and 21 encoding the Src homology 2 domain. The most common mutation hotspots are localized at amino acids D661 and Y640, accounting for two-thirds of detected mutations.\(^{38}\) Activating mutations outside the Src homology 2 domain are rarely detected and are located in the DNA-binding and coiled-coil domain of Stat3.\(^{39}\) The use of deep sequencing has demonstrated that a substantial proportion of patients with LGL leukemia have multiple Stat3-mutated lymphocyte clones mimicking the clonal diversity observed in patients with acute leukemia.\(^{40}\)

Stat3 mutation cannot fully explain the activation of Jak/Stat3 pathway in all LGL leukemia cases. IL-6 is a pro-inflammatory cytokine capable of activating the Jak/Stat3 pathway. Increased levels of this cytokine have been found in the sera of patients with LGL leukemia. When the action of this cytokine is blocked, LGL cell apoptosis is restored. Suppressor of cytokine signaling 3 (Socs3) induces negative feedback on Stat3 and was found to be down-expressed in patients with LGL. However, no Socs3 mutation could be found in patients with LGL leukemia.\(^{41}\) Whole-exome sequencing was undertaken in a 19-patient series, and several mutations leading to JAK/Stat pathway activation were found, including Stat3 wild-type patients.\(^{42,43}\)

Whether Stat3 mutations are correlated with specific clinicobiologic features remains uncertain, and results are often contradictory. Recently, Teramo et al.\(^{44}\) published a correlation between LGL phenotype and Stat3 status: patients with CD8+/CD16−/CD56+ T-LGL leukemia frequently have more Stat3 mutations and neutropenia, whereas those with CD4+/CD8+ T-LGL leukemia are devoid of Stat3 mutations but characterized by Stat5b mutations. A particular Stat3 mutation, Y640F, was found to be predictive of responses to initial therapy with methotrexate (MTX) in a prospective clinical study.\(^{45}\) Mutations in tumor necrosis factor alpha–induced protein 3, coding for A20, a negative regulator of nuclear factor kB signaling, appears to be another recurrent mutation in LGL leukemia, described in 3 of 39 patients in one series.\(^{46}\) More recently, somatic mutations in common “myeloid” genes were found in patients with LGL leukemia without morphologic presence of MDS. Aberrant myeloid clones may promote LGL development in some elderly patients.\(^{47}\)

Leukemic LGLs are known to be resistant to Fas-mediated apoptosis. Apoptosis is restored using IL-2 signaling, suggesting an inhibition mechanism instead of a defect of this pathway.\(^{48}\) More recently, a correlation was found between Stat3 activation and the presence of Fas ligand, mainly in CD8+/CD16−/CD56− patients(Fig. 4).\(^{44}\)

### TREATMENT FOR LGL LEUKEMIA

Immunosuppressive therapy is the backbone of the treatment for LGL leukemia. Sixty percent of patients requiring therapy are treated as soon as the diagnosis is made. T-LGL leukemia and NK-LGL leukemia share the same treatment options.\(^{49}\) Indications for treatment include severe neutropenia (absolute neutrophil count < 0.5 × 10^9/L), moderate neutropenia (absolute neutrophil count 0.5 × 10^9/L to 1 × 10^9/L) associated with recurrent infections, symptomatic or transfusion-dependent anemia, and associated autoimmune conditions requiring therapy.\(^{50}\)

#### First-Line Therapy

First-line therapy relies on single immunosuppressive oral agents: MTX (10 mg/m^2 per week), cyclophosphamide (100 mg/d), or ciclosporin A (3 mg/kg per day). Before assessing response, patients should be treated for at least 4 months. Treatment efficiency is related in several retrospective series, but only a few prospective trials are available. First-line therapy results are detailed in Table 3 (only series including more than 10 patients are reported). MTX and cyclophosphamide are the main immunosuppressive agents used in treating patients with LGL leukemia. Overall response rates do not exceed 35%. Deep sequencing analyses of residuals LGL clones reveals that cyclophosphamide may eradicate LCL clones, providing durable response, whereas MTX and ciclosporin A treatment are associated with the persistence of leukemic clones.\(^{40}\) Those results remain to be validated in prospective trials. An important randomized trial (NCT01976182) investigating first-line MTX versus cyclophosphamide is ongoing in France and will hopefully determine the best choice of initial therapy in this disease. In case of anemia, ciclosporin A may be preferentially proposed as first- or second-line therapy,\(^{51}\) especially for patients with pure red cell aplasia. Overall, clinical responses occur with these three drugs, but relapses frequently occur, due to the persistence of leukemic LGL clone.

#### Second-Line Therapy

Purine analogs (fludarabine, cladribine, deoxycoformycin, and bendamustine) may be proposed for disease refractory to first-line therapies. These molecules were reported to give promising results (overall response rate, 79%), though in only a few patients.\(^{57}\)

Polychemotherapy based on CHOP-like (cyclophosphamide, doxorubicin, vincristine, and prednisone) or cytosine arabinoside–containing regimens is inefficient and toxic in patients with chronic LGL leukemia. Those intensive therapies should be proposed in aggressive LGL leukemia cases. In some patients with refractory disease, stem cell therapy...
may be considered. In a series of 15 patients receiving autologeneic or allogeneic stem cell therapy for LGL leukemia, 6 patients remained disease free after transplantation. Alemmtuzumab has been proposed for refractory disease in very limited series, with an overall response rate of 60%, but the toxicity and availability of this drug limit its use. Rituximab, a specific anti-CD20 monoclonal antibody, has been paradoxically used in patients with both rheumatoid arthritis and LGL leukemia with apparent responses.

**FIGURE 4. Pathogenesis of LGL Leukemia**

The first step of large granular lymphocyte (LGL) leukemia proliferation is related to chronic antigen stimulation leading to a polyclonal expansion. Clonal proliferation is sustained by interleukin (IL–15 proinflammatory cytokine and platelet-derived growth factor (PDGF) promoting natural killer (NK) cell or leukemic LGL survival. The hallmark of LGL proliferation is the constitutive activation of Stat3. This activation is explained by common somatic gain-of-function Stat3 mutations in about 40% of patients with LGL leukemia. Moreover, LGL leukemia cells are resistant to Fas-mediated apoptosis. Soluble Fas acts as a decoy receptor able to inhibit Fas-dependent apoptosis. A recurrent nonsynonymous mutation in the gene encoding a nuclear factor κB (NF-κB) signaling inhibitor, tumor necrosis factor alpha–induced protein 3 (TNFAIP3), is found in 8% of patients with LGL leukemia and STAT5b mutation in about 2% of patients.

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Type of Study</th>
<th>Number of Patients</th>
<th>ORR, % (No. of Patients)</th>
<th>CR (No. of Patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Sanikommu et al (2018)</td>
<td>Retrospective</td>
<td>34</td>
<td>44% (15)</td>
</tr>
<tr>
<td></td>
<td>Bareau et al (2010)</td>
<td>Retrospective</td>
<td>36</td>
<td>44% (16)</td>
</tr>
<tr>
<td></td>
<td>Loughran et al (1994)</td>
<td>Prospective</td>
<td>10</td>
<td>60% (6)</td>
</tr>
<tr>
<td></td>
<td>Loughran et al (2015)</td>
<td>Prospective</td>
<td>54</td>
<td>38% (21)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Sanikommu et al (2018)</td>
<td>Retrospective</td>
<td>22</td>
<td>47% (10)</td>
</tr>
<tr>
<td></td>
<td>Moignet et al (2014)</td>
<td>Retrospective</td>
<td>45</td>
<td>72% (32)</td>
</tr>
<tr>
<td></td>
<td>Poullot et al (2014)</td>
<td>Retrospective</td>
<td>13</td>
<td>69% (9)</td>
</tr>
<tr>
<td></td>
<td>Dhodapkar et al (1994)</td>
<td>Retrospective</td>
<td>16</td>
<td>63% (10)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Sanikommu et al (2018)</td>
<td>Retrospective</td>
<td>44</td>
<td>45% (20)</td>
</tr>
<tr>
<td></td>
<td>Osuji et al (2006)</td>
<td>Retrospective</td>
<td>14</td>
<td>92% (13)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete responses; ORR, overall response rate.

Only series including more than 10 patients are reported.
Splenectomy may be proposed in case of symptomatic splenomegaly associated or not with cytopenias, with an overall response rate of 56%, but sustained responses are frequent. 60

Emerging Therapies
Considering the pathogenesis of LGL leukemia, different specific inhibitors were tested in patients with LGL leukemia. Inhibition of IL-15 trans presentation in CD122+ cells by HuMikb1 was tested in a clinical trial (NCT00076180), without clinical efficiency. Targeting Ras activation, a farnesyltransferase inhibitor (tipifarnib) was also tested in an eight-patient series but without clinically convincing results. A phase I study in an anti-CD2 monoclonal antibody (siplizumab) was conducted in 2005 in patients with relapsed or refractory CD21 T-cell lymphoma or leukemia, including T-LGL leukemia (NCT00123942). To our knowledge, the results of this trial have not been published.

Jak/Stat3 inhibition could be a good therapeutic option in patients with LGL leukemia. Tofacitinib citrate (CP690550), a Jak3-specific inhibitor, has demonstrated impressive activity in refractory rheumatoid arthritis.61 This specific inhibitor has been tested in nine patients with refractory LGL leukemia and rheumatoid arthritis, and hematologic response was observed in six patients, with improvement in neutropenia observed in five of seven patients.62

The novel multicytokine inhibitor BNZ-1 could be promising for patients with LGL leukemia. It selectively inhibits IL-2 and IL-15 and to a lesser degree IL-9 signaling without affecting IL-4, IL-7, or IL-21.63 In a phase I dose escalation trial, it presented as a highly active, selective immunomodulator that safely decreases T regulatory cells, NK cells, and memory T cells, while leaving the major leukocyte populations unaffected, and it will be tested in patients with LGL leukemia in a phase I/II trial (NCT03239392).

References


New Treatment Algorithms in Hodgkin Lymphoma: Too Much or Too Little?

Michael A. Spinner, MD, Ranjana H. Advani, MD, Joseph M. Connors, MD, Jacques Azzi, MD, and Catherine Diefenbach, MD

OVERVIEW

Hodgkin lymphoma treatment continues to evolve as new means of assessing response to treatment, new appreciation of important risk factors, and more effective therapeutic agents become available. Treatment algorithms integrating functional imaging now provide the opportunity to modify therapy during its delivery, allowing adjustment of duration and intensity of chemotherapy and rationale identification of patients who may benefit from the addition of therapeutic irradiation. Novel agents, including the antibody drug conjugate brentuximab vedotin and checkpoint inhibitors such as nivolumab and pembrolizumab can improve the effectiveness of treatment while keeping toxicity within acceptable limits. Carefully designed clinical trials permit the identification of superior approaches in which efficacy is enhanced and toxicity minimized. Clinicians treating patients with Hodgkin lymphoma now have access to novel treatment approaches, which will require detailed assessment of each patient and careful discussion of the goals and risks of treatment at the time of planning primary treatment, again during delivery of that treatment as data indicating ongoing effectiveness become available, at the conclusion of initial intervention, and, when the need arises, at the time of recurrence of disease.

Patients with early-stage Hodgkin lymphoma (Ann Arbor stage I or II; ESHL) have excellent outcomes with contemporary therapy. Recognition of late effects of extended field radiotherapy and excellent outcomes with involved field radiotherapy (IFRT) in combination with chemotherapy established combined modality therapy (CMT) with 4× doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy IFRT as a gold standard with a 12-year progression-free survival (PFS) and overall survival (OS) of 94%.1-5 Outcomes vary based on the frequency of absence (favorable) or presence (unfavorable) of clinical risk factors, which differs among study groups (Table 1).6,7 Within the caveats of retrospective analyses, a recent Cochrane review, meta-analysis, and registry data suggest superior PFS and OS with CMT for ESHL compared with either radiotherapy or chemotherapy alone.8-12 Observational data suggest that IFRT may reduce the risk of secondary breast cancer.13,14 In this review, we summarize studies in the CT and PET eras, which have focused on fine-tuning standard CMT to avoid giving too much therapy for favorable patients or too little therapy for unfavorable patients.

COMBINED MODALITY THERAPY IN THE CT ERA

Randomized trials in the CT era are summarized in Table 2.15-20 For favorable risk disease, efforts by the German Hodgkin Study Group (GHSG) HD10 trial to avoid giving too much treatment established 2× ABVD plus 20 Gy IFRT as an effective regimen, with equivalent efficacy and reduced toxicity compared with 4× ABVD plus 30 Gy IFRT.17 In a recent update, results were durable with a 10-year PFS of 87% and OS of 94% and no difference in the risk of second cancers.19 Interestingly, late relapse (> 5 years) was more frequent in patients with favorable disease (15-year cumulative incidence 5.3% vs. 3.9%; p = .01) and underscores the importance of long-term follow-up.21 Attempts to reduce chemotherapy intensity by omitting bleomycin or dacarbazine from ABVD in the HD13 trial resulted in impairment of disease control, with a 4% and 12% reduction in 5-year PFS, respectively.15

The therapeutic priority for unfavorable disease has been to increase treatment efficacy, and several trials investigated incorporating escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP). The GHSG HD11 and European Organization for Research and Treatment of Cancer (EORTC) H9U trials compared 4× escalated BEACOPP plus 30 Gy IFRT to 4× ABVD plus 30 Gy IFRT and failed to show a marked difference in PFS or OS.16,18 At 10 years, results were durable, with a PFS of 83% and OS of 91% in both arms.19 The subsequent HD14 trial compared a hybrid 2 + 2 regimen...
(2× escalated BEACOPP plus 2× ABVD plus 30 Gy IFRT) to 4× ABVD plus 30 Gy IFRT and demonstrated a 6.2% improvement in 5-year PFS with the 2 + 2 regimen, no difference in OS, and greater toxicity.20

Patients who present with a bulky mass 10 cm or larger on CT or mediastinal mass ratio greater than 0.33 represent a specific group with unfavorable disease. A subset analysis of the U.S. intergroup E2496 study reported a 5-year PFS of 85% and OS of 96% with ABVD followed by 36 Gy IFRT.22 Within Europe, this subgroup is treated variably either on protocols for unfavorable or advanced-stage disease, making outcomes specific to this subset difficult to interpret. Recently, Memorial Sloan Kettering Cancer Center reported on the prognostic significance of a different definition of bulk using transverse and coronal plane measurements on CT imaging.23 Using more than 7 cm in either plane as an optimal cutoff, the 4-year PFS for bulky vs nonbulky disease was 80.5% versus 94.4%, respectively (p = .004).

Concerns over late effects led to efforts to omit radiotherapy for ESHT. Only one randomized trial has compared CMT to ABVD alone in the CT era. The HD6 trial compared 4 to 6× ABVD to subtotal nodal irradiation alone (favorable) or in combination with 2× ABVD (unfavorable).24 At 12 years, PFS was greater in the CMT arm (92% vs. 87%; p = .05); however, OS favored the use of ABVD alone due to fewer cardiac events and second cancers. Although this study is instructive and illustrates that PFS is not a reliable surrogate for OS in early-stage disease, the results have to be interpreted cautiously, as subtotal nodal irradiation is obsolete. Additionally, several deaths in the radiotherapy arm were due to reasons other than relapsed lymphoma or potential radiotherapy-related effects. A pooled retrospective analysis compared patients with nonbulky early-stage disease treated with ABVD alone in the H6 trial to patients with a similar risk profile treated in the GHSG HD10 and HD11 trials.25 Results suggested that CMT provided better disease control than ABVD alone, especially among those not achieving a complete remission on CT imaging, and OS was similar. A subgroup analysis suggested that patients achieving a complete remission on CT after 2× ABVD might not need consolidative IFRT.

### INTERIM PET RESPONSE-ADAPTED THERAPY

Efforts over the last decade have focused on tailoring therapy according to risk using an interim PET scan.26 A major objective of these trials has been to assess if radiotherapy can be omitted in interim PET-negative patients and whether intensifying therapy will improve outcomes for PET-positive patients. Key prospective trials evaluating PET response-adapted approaches are summarized in Table 3.27-29

In the U.K. RAPID trial, patients with stage I/IIA nonbulky disease received 3× ABVD followed by a PET scan.28 PET-negative patients (Deauville 1 to 2) were randomized to 30 Gy IFRT or no further therapy, whereas PET-positive patients received an additional cycle of ABVD followed by 30 Gy IFRT. In the intention-to-treat/per-protocol analyses for CMT versus chemotherapy alone, PET-negative patients had a 3-year PFS of 94.6% versus 90.8% (HR 1.75; 95% CI, 0.84–2.97; p = .16)/97.1% versus 90.8% (HR 2.36; 95% CI, 1.13–4.95; p = .02), respectively, with no difference in OS. Although these results suggest that outcomes with chemotherapy alone are excellent in approximately 90% of patients, noninferiority of chemotherapy alone could not be established.

### TABLE 1. Unfavorable Risk Factors in Early-Stage Hodgkin Lymphoma by Study Group

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>NCCN</th>
<th>EORTC</th>
<th>GHSG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>—</td>
<td>≥ 50 years</td>
<td>—</td>
</tr>
<tr>
<td>ESR, B symptoms</td>
<td>&gt; 50 mm/hour or any B symptoms</td>
<td>&gt; 50 if A, &gt; 30 if B</td>
<td>&gt; 50 if A, &gt; 30 if B</td>
</tr>
<tr>
<td>Bulky disease</td>
<td>MMR &gt; 0.33 or any site ≥ 10 cm</td>
<td>MTR &gt; 0.35</td>
<td>MMR &gt; 0.33</td>
</tr>
<tr>
<td>Nodal sites</td>
<td>&gt; 3</td>
<td>&gt; 3</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Extramodal disease</td>
<td>—</td>
<td>—</td>
<td>Any extramodal lesion</td>
</tr>
</tbody>
</table>

Abbreviations: NCCN, National Comprehensive Cancer Network; EORTC, European Organization for Research and Treatment of Cancer; GHSG, German Hodgkin Study Group; ESR, erythrocyte sedimentation rate; MMR, mediastinal mass ratio; MTR, mediastinal thoracic ratio.

### PRACTICAL APPLICATIONS

- **ESHT can be quite successfully treated with brief multiagent chemotherapy (ABVD for two cycles) followed by involved site radiotherapy.**
- **For ESHT, an acceptable alternative to brief chemotherapy plus planned involved site radiotherapy is brief chemotherapy (ABVD for 3–4 cycles), after which involved site radiotherapy is reserved solely for patients with persistent postchemotherapy PET scan–positive disease.**
- **For advanced-stage classic (CD30-positive) Hodgkin lymphoma, the combination of doxorubicin, vinblastine, dacarbazine, and brentuximab vedotin has emerged as a more effective primary chemotherapy than ABVD that can be delivered with acceptable toxicity.**
- **Patients with recurrent Hodgkin lymphoma despite optimal primary chemotherapy should be offered treatment with high-dose chemotherapy followed by ASCT unless they have a specific contraindication.**
- **Hodgkin lymphoma that recurs after ASCT usually cannot be cured but can be very usefully palliated with new agents such as brentuximab vedotin and the checkpoint inhibitors nivolumab and pembrolizumab.**
The EORTC/Lymphoma Study Association/Fondazione Italiana Linfomi H10 trial evaluated a response-adapted strategy after 2× ABVD.29 Notably, the trial used contemporaneous involved node radiotherapy (INRT), which requires a prechemotherapy PET scan for radiation planning and is associated with more precise contouring of involved nodes and reduced field size compared with IFRT.30 In the standard arm, patients received 30 Gy INRT after one to two additional cycles of ABVD depending on risk. In the experimental arm, patients with a negative PET scan (Deauville 1 to 2) received two to four additional cycles of ABVD depending on risk without consolidative radiotherapy. In PET-positive patients, chemotherapy was intensified to 2× escalated BEACOPP followed by 30 Gy INRT. For PET-negative patients, the final analysis confirmed that CMT resulted in a substantial improvement in 5-year PFS by 12% in favorable risk patients (HR 15.8; 95% CI, 3.79–66.07) and 3% for unfavorable risk patients (HR 1.45; 95% CI, 0.84–2.50).27 For PET-positive patients, 5-year PFS was 13% greater with intensified therapy compared with standard therapy with ABVD (HR 0.42; 95% CI, 0.23–0.74; p = .002).

The Cancer and Leukemia Group B-50604 trial also evaluated an adaptive design in patients with early-stage nonbulky disease.31 In contrast to the latter trials, PET negativity was defined as Deauville 1 to 3. After 2× ABVD, PET-negative patients received two additional cycles of ABVD without consolidative radiotherapy, whereas PET-positive patients received 2× escalated BEACOPP plus 30 Gy IFRT. At interim analysis, 3-year PFS was 92% and 66% in PET-negative and -positive patients, respectively, suggesting that intensifying therapy to escalated BEACOPP is insufficient to rescue patients with Deauville 4 to 5.

Cumulatively, the two randomized PET-adapted trials do not seem to identify a group of patients for whom radiotherapy can be omitted without some reduction in PFS. OS is excellent, but follow-up of both studies is too short to inform long-term outcomes. Recently, radiotherapy fields have further evolved from IFRT to involved site radiotherapy (ISRT), in which the field size is restricted to the pretreatment volume of involved nodal sites.30 A retrospective study evaluated outcomes in patients with early-stage favorable disease treated with 2× ABVD followed by a PET scan and 20 Gy ISRT in patients with a Deauville score of 1 to 2.32 At a median follow-up of 45 months, outcomes were excellent, with a 4-year PFS of 93% and OS of 100%, suggesting that ISRT can replace IFRT without impacting outcomes.

The ongoing GHSG HD16 trial in favorable patients is evaluating 2× ABVD plus 20 Gy IFRT (standard arm) to a PET-guided experimental arm of 2× ABVD followed by observation (PET-negative) or 20 Gy IFRT (PET-positive). The GHSG HD17 trial is investigating the potential equivalence of IFRT and INRT. Results of these two trials are awaited. The challenge is how does one apply these various results in day-to-day practice? Clearly all studies suggest that CMT is associated with a small but noteworthy improvement in PFS in the 3% to 12% range. Radiotherapy is appropriate

### TABLE 2. Trials Evaluating Combined Modality Therapy for Early-Stage Hodgkin Lymphoma in the CT Era

<table>
<thead>
<tr>
<th>Trial</th>
<th>Disease Risk</th>
<th>Patient Number</th>
<th>Chemotherapy Regimen</th>
<th>Radiotherapy Field and Dose</th>
<th>OS, %</th>
<th>PFS, %</th>
<th>PFS HR (95% CI)</th>
<th>Median Follow-up, Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>GHSG HD10</td>
<td>Favorable</td>
<td>1,190</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>87</td>
<td>1.0 (0.6–1.5)</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 ABVD</td>
<td>IFRT 20 Gy</td>
<td>94</td>
<td>87</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GHSG HD11</td>
<td>Unfavorable</td>
<td>1,395</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>91</td>
<td>83</td>
<td>1.5 (1.1–2.2)</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 ABVD</td>
<td>IFRT 20 Gy</td>
<td>90</td>
<td>75</td>
<td>1.1 (0.7–1.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 Esc BEACOPP</td>
<td>IFRT 30 Gy</td>
<td>91</td>
<td>83</td>
<td>1.2 (0.8–1.7)</td>
<td></td>
</tr>
<tr>
<td>GHSG HD13</td>
<td>Favorable</td>
<td>1,502</td>
<td>2 ABVD</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>98</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 ABV</td>
<td>IFRT 30 Gy</td>
<td>90</td>
<td>98</td>
<td>2.0 (1.2–3.4)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 AVD</td>
<td>IFRT 30 Gy</td>
<td>79</td>
<td>98</td>
<td>2.3 (1.3–4.0)</td>
<td></td>
</tr>
<tr>
<td>GHSG HD14</td>
<td>Unfavorable</td>
<td>1,528</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>97</td>
<td>89</td>
<td>0.5 (0.3–0.7)</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2 Esc BEACOPP + 2 ABVD</td>
<td>IFRT 30 Gy</td>
<td>97</td>
<td>95</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC H9-U</td>
<td>Unfavorable</td>
<td>808</td>
<td>4 ABVD</td>
<td>IFRT 30 Gy</td>
<td>94</td>
<td>86</td>
<td></td>
<td>90</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4 Esc BEACOPP</td>
<td>IFRT 30 Gy</td>
<td>93</td>
<td>89</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 ABVD</td>
<td>IFRT 30 Gy</td>
<td>93</td>
<td>90</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Esc, escalated; NR, not reported.
for patients with bulky disease and those with a positive interim or end-of-therapy PET scan. To help individualize therapy, a thoughtful discussion is required in which other factors also must be considered to assess risk from primary therapy (i.e., the anatomic extent of disease and resultant normal tissue exposure to radiotherapy, cumulative toxicity of additional cycles of chemotherapy if radiotherapy is to be avoided, and added toxicity from salvage therapy). Therefore, chemotherapy alone may be preferred over CMT for a young woman younger than age 35 with mediastinal or axillary disease to avoid the risk of breast cancer. In contrast, for a young patient with bilateral neck disease, 2× ABVD plus 20 Gy ISRT would be a very effective approach.

For patients with bulky disease and those with a positive interim or end-of-therapy PET scan. To help individualize therapy, a thoughtful discussion is required in which other factors also must be considered to assess risk from primary therapy (i.e., the anatomic extent of disease and resultant normal tissue exposure to radiotherapy, cumulative toxicity of additional cycles of chemotherapy if radiotherapy is to be avoided, and added toxicity from salvage therapy). Therefore, chemotherapy alone may be preferred over CMT for a young woman younger than age 35 with mediastinal or axillary disease to avoid the risk of breast cancer. In contrast, for a young patient with bilateral neck disease, 2× ABVD plus 20 Gy ISRT would be a very effective approach.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, CMT remains the current standard of care for the majority of patients with ESHL. Ongoing studies continue to focus on reducing toxicity while maintaining or improving long-term cure rates. Radiotherapy doses and field size have evolved significantly over the past several decades and are expected to have a lower risk of cardiovascular disease and second cancers.30,33 Recent studies incorporating brentuximab vedotin (BV)34,35 and the PD-1 inhibitors nivolumab and pembrolizumab are summarized in Table 4. Pretreatment risk assessment with metabolic tumor volume, total lesion glycolysis, and serum thymus and activation-regulated chemokine levels may help define

### Table 3. Prospective Trials Evaluating PET-Adapted Approaches for Early-Stage Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Timing of PET After ABVD</th>
<th>PET-Negative Deauville Score</th>
<th>Percent PET-Negative</th>
<th>Treatment Regimens</th>
<th>PFS, %</th>
<th>HR (95% CI)</th>
<th>Median Follow-up, Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>U.K. RAPID27 (602 patients)</td>
<td>3 cycles</td>
<td>1–2</td>
<td>75</td>
<td>3 ABVD + 30 Gy IFRT (standard)</td>
<td>94.6 (ITT), 97.1 (PP)</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 ABVD (PET−)</td>
<td>90.8 (ITT), 90.8 (PP)</td>
<td>ITT: 1.57 (0.84–2.97)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 ABVD + 30 Gy IFRT (PET+)</td>
<td>87.6 PP: 2.36 (1.13–4.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC H10F28,29 (754 patients)</td>
<td>2 cycles</td>
<td>1–2</td>
<td>87</td>
<td>3 ABVD + 30 Gy INRT (standard)</td>
<td>99.0</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4 ABVD (PET−)</td>
<td>87.1</td>
<td>15.8 (3.8–66.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy INRT (PET+)</td>
<td>90.6*</td>
<td>0.42 (0.23–0.74)</td>
<td></td>
</tr>
<tr>
<td>EORTC H10U28,29 (1,196 patients)</td>
<td>2 cycles</td>
<td>1–2</td>
<td>78</td>
<td>4 ABVD + 30 Gy INRT (standard)</td>
<td>92.1</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6 ABVD (PET−)</td>
<td>89.6</td>
<td>1.45 (0.8–2.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy INRT (PET+)</td>
<td>90.6*</td>
<td>0.42 (0.23–0.74)</td>
<td></td>
</tr>
<tr>
<td>CALGB-5060430 (164 patients)</td>
<td>2 cycles</td>
<td>1–3</td>
<td>91</td>
<td>4 ABVD (PET−)</td>
<td>92</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2 ABVD + 2 EB + 30 Gy IFRT (PET+)</td>
<td>66</td>
<td>6.0 (1.8–20.1)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes both favorable and unfavorable risk patients with a positive interim PET scan.

Abbreviations: ITT, intention to treat; PP, per protocol; EB, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CALGB, Cancer and Leukemia Group B.

### Table 4. Trials Incorporating Novel Agents Into Frontline Therapy for Early-Stage Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Population</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01868451</td>
<td>Unfavorable risk</td>
<td>BV-AVD + CVRT (30 Gy)</td>
</tr>
<tr>
<td>NCT03004833</td>
<td>Unfavorable risk</td>
<td>Nivolumab-AVD + IFRT (30 Gy)</td>
</tr>
<tr>
<td>NCT03226249</td>
<td>Favorable or unfavorable</td>
<td>Pembrolizumab-AVD</td>
</tr>
<tr>
<td>NCT03233347</td>
<td>Stage I to II nonbulky</td>
<td>BV-AVD + nivolumab consolidation</td>
</tr>
<tr>
<td>NCT02758717</td>
<td>Age &gt; 60</td>
<td>BV + nivolumab</td>
</tr>
<tr>
<td>NCT01716806</td>
<td>Age &gt; 60</td>
<td>BV + nivolumab, bendamustine, or dacarbazine</td>
</tr>
<tr>
<td>NCT02191930</td>
<td>Age &gt; 60, stage II bulky</td>
<td>BV + cyclophosphamide, doxorubicin, and prednisone</td>
</tr>
<tr>
<td>NCT02298283</td>
<td>PET-positive after 2 ABVD</td>
<td>BEACOPP + IFRT (30 Gy) + BV consolidation</td>
</tr>
</tbody>
</table>

Abbreviation: CVRT, conformational volume radiotherapy.
higher-risk patients at diagnosis in whom alternative approaches can be considered. Long-term follow-up is needed to determine the impact of these novel approaches.

NEW RISK-ADAPTED TREATMENT STRATEGIES IN ADVANCED-STAGE HODGKIN LYMPHOMA

The success that has been achieved in treating HL has provided a paradigm on which much of modern systemic oncologic treatment is based. It is imperative to achieve the greatest possible efficacy while minimizing toxicity, both during and after primary treatment. Randomized prospective clinical trials have proven pivotal to support evidence-based treatment planning complemented by the population-based evaluations needed to demonstrate effective translation into real-world settings.

STAGING, PROGNOSTIC FACTORS, AND RISK ASSESSMENT

Staging of HL is based on the Ann Arbor system, with the addition of a definition of bulky disease often referred to as the Cotswold modification. PET employing 18F-fluorodeoxyglucose has become essential not only to establish stage at diagnosis but also to provide a running assessment of treatment effectiveness both during and at the conclusion of primary treatment. Especially in the treatment of patients with advanced-stage disease, prognostic factor scoring systems can be helpful both in assessing and comparing clinical trial results and identifying patients at high risk of relapse. A robust prognostic model that identifies patients with differing risks of primary treatment failure was initially based on outcomes in approximately 5,000 patients with advanced-stage HL, most of whom had been treated with ABVD. Seven independent predictors of decreased likelihood of freedom from progression—sex, age, stage, hemoglobin level, white blood cell count, lymphocyte count, and serum albumin—can be combined in an International Prognostic Factors Score (IPS) to identify subgroups of patients with varying likelihood of freedom from progression based on the number of factors present at diagnosis (Table 5). Improvements in accuracy of diagnosis, staging based on PET, supportive care, and widespread use of high-dose chemotherapy and autologous hematopoietic stem cell transplantation (ASCT) for relapsed disease have lessened the discriminatory power of the IPS, as evidenced in the results we have seen at the BC Cancer Agency with 675 consecutive patients treated with ABVD or equivalent chemotherapy through 2009. The spread in 5-year freedom from progression has narrowed to 17% spread, ranging from 83% to 66%, and for the 94% of patients with advanced-stage HL who present with IPS of 0 to 4, the 5-year OS has improved to approximately 90%. This change demonstrates that as overall treatment strategies improve, the impact of clinical prognostic scoring systems diminishes.

A large number of biologic characteristics of HL (biomarkers) with possible impact on risk have been identified, including a variety of biomarkers: antigens expressed on the HL Reed-Sternberg (HRS) cells; antigens expressed on circulating lymphocytes; antigens expressed on microenvironmental cells within the tumor; circulating biomarkers detectable in the serum; gene expression profiles of biopsied tumors; and specific germline polymorphisms. All are of interest; however, turning these interesting biologic observations into clinically relevant biomarkers for purposes of treatment planning has proven difficult, and, at present, they do not appear ready for integration into standard management.

A different set of risk factors relevant to HL are those that become evident during treatment. Treatment of advanced-stage HL is typically takes at least 6 to 8 months to complete. Poor quality of response during the delivery of multiple cycles of chemotherapy or absence of a complete response (CR) at the end of planned chemotherapy may identify patients with higher risk of relapse. The wide availability of PET imaging provides the opportunity to determine its usefulness in the management of both limited-stage HL and advanced-stage disease.

POSITIVE INTERIM PET SCAN AS A RISK FACTOR FOR ADVANCED-STAGE HODGKIN LYMPHOMA

ABVD is the only multiagent chemotherapy program for which interim PET has been evaluated extensively. Table 6 shows the outcome for patients treated with ABVD for advanced-stage HL, comparing results for those with a positive versus negative interim PET during ABVD chemotherapy. A negative interim PET is found in approximately 80% of patients, appears to be strongly predictive for a favorable outcome, and may largely override the prognostic impact of the IPS. However, for the approximately 20% of patients with a positive interim PET, the impact of a growing body of evidence suggests that the negative prognostic impact of a positive interim PET can be at least partially overcome by switching to intensified treatment such as escalated BEACOPP after a positive interim PET. This switch to intensified treatment may as much as double 2- to 3-year failure-free survival (Table 7). This substantial improvement in freedom from treatment failure is obtained at the cost of much higher toxicity using the alternative regimen, making the strategy of interim PET-guided intensification of treat-

TABLE 5. Prognostic Factors Indicating Decreased Probability of Freedom From Progression in Advanced Hodgkin Lymphoma Treated With ABVD or an Equivalent Regimen

<table>
<thead>
<tr>
<th>Factor</th>
<th>Adverse Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender male</td>
<td>Age &gt; 45</td>
</tr>
<tr>
<td>Stage IV</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; 105 g/L</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>&gt; 15 x 109/L</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td>&lt; 0.6 x 109/L or &lt; 8% of the white cell differential</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>&lt; 40 g/L</td>
</tr>
</tbody>
</table>
ment one that must be compared with a strategy of reserving intensification, with high-dose chemotherapy and ASCT, until definite progression occurs following completion of standard-dose chemotherapy.

An alternative use of interim PET scan is to justify de-escalation of treatment intensity when PET negativity has been achieved. In such a strategy, treatment starts with intensified chemotherapy, such as escalated BEACOPP, and switches to lower intensification, perhaps ABVD, after an interim PET scan documents a high-quality response. The potential pros and cons of such a strategy are discussed below in the section on new approaches.

**POSITIVE END-OF-CHEMOTHERAPY PET SCAN AS A RISK FACTOR FORADVANCED-STAGE HODGKIN LYMPHOMA**

Persistence of viable tumor despite completion of planned chemotherapy for advanced HL is an obvious indicator of treatment failure and risk factor for recurrence. Although adding irradiation after the achievement of complete remission using multiagent chemotherapy for advanced-stage HL does not improve long-term outcome, the apparent ability of PET to identify patients with persistent active lymphoma has led to the advocacy of postchemotherapy irradiation when persistent disease is strongly suggested by a positive PET scan. Adding involved field radiation to a postchemotherapy residual PET-positive mass appears to improve a patient’s outcome to the same level as is achieved by patients who have a complete remission with either no residual mass or a PET-negative mass.

**NEW APPROACHES**

Over the past 2 decades, two different approaches to overcoming treatment resistance in advanced-stage HL have emerged. The GHSG initially developed and refined a dose-escalated and accelerated chemotherapy program, escalated BEACOPP. Through a series of logical, well-designed clinical trials, this group demonstrated the superiority of escalated BEACOPP over regimens such as ABVD in terms of PFS, but documentation of superior OS has proven elusive, and many clinicians consider the increased short- and long-term toxicity of escalated BEACOPP too great to justify its use. More recently, however, a PET-adapted strategy in which a negative interim PET scan is used to prompt de-escalation to a reduced number of cycles of escalated BEACOPP has shown substantial promise. In the GHSG HD18 trial, 70% of patients with advanced-stage HL reached a PET-negative response after two cycles of escalated BEACOPP. Those then randomly assigned to complete treatment with two more cycles of escalated BEACOPP had a 5-year PFS of 92%, which was just as good as those randomized to complete treatment with four more cycles of escalated BEACOPP. Other investigators have evaluated de-escalation to regimens such as ABVD and in smaller, nonrandomized experiences have also shown excellent outcomes for patients with negative interim PET scans.

An alternative approach to improving results for patients with advanced-stage HL has investigated the usefulness of adding a new therapeutic agent to the standard backbone of ABVD. The ECHELON-1 trial randomized patients to standard ABVD versus doxorubicin, vinblastine, and dacarbazine (AVD) plus BV, an antibody drug conjugate directed against the CD30 antigen. The novel combination induced a superior freedom from treatment failure of 82% compared with 77% for those treated with standard ABVD. Of note, in the ECHELON-1 trial, treatment was not guided by interim PET. All patients received their randomly assigned chemotherapy regimen. The novel regimen, AVD plus BV, appeared equally superior across multiple subgroups of patients, including those with high IPS scores, stage IV disease, and those with bone marrow or multiple extranodal sites of disease.

**OVERALL TREATMENT STRATEGY AND FUTURE DIRECTIONS**

The treatment of advanced-stage HL continues to evolve. Currently, the two best strategies that have emerged from clinical trials are either interim PET-guided escalation or de-escalation approaches or integration of the novel agent BV into primary chemotherapy. In the absence of a head-to-head comparison of these strategies, the final choice will appropriately remain with the treating specialist and should reflect careful discussion of the pros and cons of

### TABLE 6. Prognostic Impact of Interim PET Scan for Patients With Advanced-Stage Hodgkin Lymphoma Treated With ABVD

<table>
<thead>
<tr>
<th>Interim PET</th>
<th>N (%)</th>
<th>3-Year FFS, %</th>
<th>Treatment Failed, n (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>215 (83)</td>
<td>95</td>
<td></td>
<td>Biggi et al</td>
</tr>
<tr>
<td>Positive</td>
<td>45 (17)</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>210 (81)</td>
<td>11 (5)</td>
<td></td>
<td>Gallamini et al</td>
</tr>
<tr>
<td>Positive</td>
<td>50 (19)</td>
<td>43 (86)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>61 (79)</td>
<td>3 (5)</td>
<td></td>
<td>Hutchings et al</td>
</tr>
<tr>
<td>Positive</td>
<td>16 (21)</td>
<td>11 (18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Eleven patients did not receive the randomly assigned escalation of chemotherapy due to patient refusal.

### TABLE 7. Impact of Chemotherapy Escalation Based on Interim PET Scan for Patients With Advanced-Stage Hodgkin Lymphoma Treated Initially With ABVD: Phase II and Retrospective Trial Results

<table>
<thead>
<tr>
<th>Interim PET</th>
<th>N (%)</th>
<th>2-Year PFS, %</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>271 (82)</td>
<td>82</td>
<td>Press et al</td>
</tr>
<tr>
<td>Positive</td>
<td>60 (18)</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>41 (84)</td>
<td>82</td>
<td>Ganesan et al</td>
</tr>
<tr>
<td>Positive</td>
<td>8 (16)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Approximately 80%</td>
<td>95</td>
<td>Gallamini et al</td>
</tr>
<tr>
<td>Positive</td>
<td>Approximately 20%</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>
the different strategies. This final choice should be based on a full assessment of how to achieve the greatest efficacy while minimizing both short- and long-term toxicity. Future improvements in these already excellent results will likely involve further integration of novel agents, among which the checkpoint inhibitors appear to have the greatest potential.

**BEYOND TRANSPLANT: NOVEL THERAPIES IN RELAPSED AND REFRACTORY HL**

Prior to 2011, treatment options for patients with relapsed/refractory HL were limited to salvage chemotherapy and ASCT. With the approval of the antibody drug conjugate BV in 2011 and the immune checkpoint inhibitors nivolumab and pembrolizumab in 2016 and 2017, respectively, a new frontier has arrived. These new treatment modalities are changing the standard of care for patients with relapsed/refractory HL whose options were previously limited to cytotoxic chemotherapy. Still, many challenges remain as we study how to optimize the implementation of these therapies, including: how to determine which patients will benefit the most from which treatments, how to combine these agents with other novel agents or with standard chemotherapy, and whether these therapies can be incorporated into earlier lines of treatment. Given the curability of ASCT in up to 50% of relapsed/refractory HL, how should these therapies be sequenced with autologous and allogeneic SCT? As other novel therapies and novel combinations currently under investigation obtain approval, how will these be prioritized, sequenced, or combined with existing agents? Although this is an extremely exciting time for relapsed/refractory HL, the answers to these questions will hopefully advance still further the goals of increasing cure and minimizing toxicity for patients with relapsed/refractory HL.

**BV**

BV is an anti-CD30 monoclonal antibody attached to a cytotoxic antimitotubule agent monomethyl auristatin. BV was U.S. Food and Drug Administration approved for patients with relapsed/refractory HL who have failed either ASCT or at least two chemotherapy regimens, based on the pivotal phase II trial, which treated 102 patients with relapsed/refractory HL who have failed either ASCT or at least chemotherapy. It is currently under investigation obtain approval, how will these be prioritized, sequenced, or combined with existing agents? Although this is an extremely exciting time for relapsed/refractory HL, the answers to these questions will hopefully advance still further the goals of increasing cure and minimizing toxicity for patients with relapsed/refractory HL. BV was approved for ASCT in up to 50% of relapsed/refractory HL, how should these therapies be sequenced with autologous and allogeneic SCT? As other novel therapies and novel combinations currently under investigation obtain approval, how will these be prioritized, sequenced, or combined with existing agents? Although this is an extremely exciting time for relapsed/refractory HL, the answers to these questions will hopefully advance still further the goals of increasing cure and minimizing toxicity for patients with relapsed/refractory HL.

**CHECKPOINT INHIBITORS**

HRS tumor cells comprise a small fraction (0.1%) of the cells in the HL microenvironment. Driven mainly by somatically acquired alterations of chromosome 9p24.1/CD274(PD-L1)/PDCD1LG2(PD-L2), HRS cells overexpress PD-L1 and PD-L2, which interact with PD-1 on peritumoral lymphocytes in the HL microenvironment and induce chronic activation and exhaustion.61-64 PD-L1 overexpression is not limited to HRS cells, but has also been reported in nonmalignant tumor-associated macrophages that are localized around PD-L1+ HRS cells.65-67 Nivolumab and pembrolizumab are immunoglobulin G4 monoclonal anti–PD-1 antibodies approved by the U.S. Food and Drug Administration for the treatment of relapsed/refractory HL. In the initial CheckMate 039 trial, 23 patients with HL who progressed post-ASCT (78%) or BV (78%) were treated with nivolumab; a high ORR of 87% and PFS of 86% at 24 weeks was demonstrated.68 Nivolumab was approved based on the CheckMate 205 trial, in which 243 patients with relapsed/refractory HL who had failed ASCT were treated with nivolumab monotherapy, with an ORR of 69%, a CR of 16%, and overall median PFS of 15 months. These heavily pretreated patients were divided into three cohorts according to their BV status, with a slightly higher CR rate for the patients not previously treated with BV as compared with patients who received BV before or after ASCT (29% vs. 12% and 13%, respectively).69 Pembrolizumab was approved based on the KEYNOTE-87 trial that divided 210 patients with relapsed/refractory HL into three cohorts according to...
previous treatment with ASCT and/or BV, with all three cohorts showing an ORR of 69% and a CR of 22%.70

Both PD-1 inhibitors represent a noteworthy advance in the treatment of relapsed/refractory HL. However, the CR rate with monotherapy to both agents is modest, and relapses to these agents are seen even beyond 2 years. Ideally, rational combinations combining these with other agents may both deepen response and improve durability for more patients.

**COMBINATION THERAPIES**

Combination therapies are developed with the goal of choosing agents with a strong scientific rationale or complementary mechanisms of action and with toxicities that do not overlap. Bendamustine was combined with BV as pretransplant salvage therapy for relapsed/refractory HL in a phase I/II trial of 55 patients and demonstrated high activity, with an ORR of 93% and CR of 74%.71 Fifty-six percent of patients experienced infusion-related reactions, which caused premature termination of treatment in 24% of patients, although premedication with antihistamines and corticosteroids appeared effective in controlling these symptoms in those who were able to continue therapy.72 These results are comparable to the standard of care for first-line salvage of relapsed/refractory HL—high-dose chemotherapy with ifosfamide, carboplatin, etoposide—and may offer an alternative out-of-hospital salvage treatment option.72

In addition to the PD-1 pathway, the CTLA-4 pathway is a key target for checkpoint blockade therapy. Neoplastic HL cells are surrounded by a microenvironment of inefficient immune cells, fibroblasts, mesenchymal cells, and microvasculature that interact with the tumor cells, promoting cell growth and creating a favorable environment for immune evasion.66,73 Both PD-1 and CTLA-4 are negative regulators of T-cell immune function. In an effort to target these nonmalignant components and alter the permissive microenvironment from protective to cytotoxic, BV has been combined with the checkpoint inhibitors ipilimumab, a fully humanized immunoglobulin G1 monoclonal antibody targeting the CTLA-4 pathway, and the PD-1 inhibitor nivolumab. Preliminary results from 21 patients treated with BV and ipilimumab on the protocol E4412 (NCT01896999) demonstrated an ORR of 71% with a CR of 48% and a median PFS of 1.02 years with a median follow-up of 0.48 years; the median OS was not reached with a median follow-up of 1.16 years.74-75 The combination of BV plus nivolumab has been explored in both E4412 and in the trial NCT02572167 in the pretransplant first salvage setting.75,76 Interim results from both studies demonstrated a high ORR and CR rate: the E4412 trial showed an ORR of 89%, a CR of 50%, and a 6-month PFS of 91% for 18 patients, whereas the NCT02572167 trial had an ORR of 82% and a CR of 61%, with the majority of non-CR patients able to undergo further therapy and continue on to ASCT.75,76 Adverse events and immune-related toxicities occurred in both studies but were limited mainly to grades 1 and 2, with nausea, fatigue, and infusion-related reactions most common. Premedication was required for infusion reactions, but once treated, patients were able to continue on treatment in both studies. One grade 5 pneumonitis was reported in E4412.

Results from these studies have been promising, but clinical experience with these combinations remains limited at present. Further investigations are needed and ongoing to determine long-term tolerability and disease control before these combinations can be integrated into standard practice.

**OTHER NOVEL THERAPIES**

Beyond BV and checkpoint blockade, there are many other promising therapies currently under exploration in early-phase clinical trials. AFM13 is a bispecific anti-CD16A, anti-CD30 antibody that binds CD16A on natural killer cells and CD30 on HL tumor cells, resulting in natural killer cell activation and tumor cell lysis. In phase I as a single agent, the response to AFM13 monotherapy was 11.5%; however, there is a scientific rationale for combining AFM13 with checkpoint blockade, and a phase I study of this combination is currently underway in relapsed/refractory HL (NCT02665650).77 Chimeric antigen receptor (CAR) T cells are autologous T cells primed to target malignant cells and have shown encouraging antitumor activity in leukemia and non-HL.78,79 In data extrapolated from mice models, a CD123 antigen was identified for use as a target for CAR T cells and showed high therapeutic activity in a preclinical in vivo model of HL.80 In a separate study, 18 heavily pretreated patients with relapsed/refractory HL received CD30-specific CAR T cells; the ORR was 39% with no CRs.78 Although HRS cells are considered CD19 negative, an ongoing pilot study evaluated CD19 CAR T cells for the treatment of relapsed/refractory HL based on the rationale that HRS precursors and other supportive immune cells promoting cancerous cell survival may harbor the CD19 antigens. Four patients received CD19 CAR T cells and showed an ORR of 50% at day 28 with acceptable toxicities; however, only one patient achieved CR and progressed after 3 months.81 Lenalidomide is an immunomodulatory drug that was studied in 36 patients with relapsed/refractory HL who received a median of four prior therapies; the ORR was 19%, and 1 patient achieved CR.82 An ongoing trial is evaluating lenalidomide as maintenance therapy for patients with relapsed HL after ASCT (NCT01207921). The mTOR inhibitor everolimus demonstrated activity in a phase II study of heavily pretreated patients with relapsed/refractory HL with an ORR of 47%, with eight out of 19 patients achieving a partial response and a median PFS of 6.2 months.83 Histone deacetylase inhibitors have also been investigated; modest single-agent activity has been seen, and they are primarily under investigation as combination strategies with other novel agents. Panobinostat, a pan-deacetylase inhibitor, was evaluated in a phase I/II study in combination with the mTOR inhibitor everolimus, and the ORR for 13 patients with relapsed/refractory HL was 46%.84

**CONCLUSION**

Recent advances in HL biology have culminated in the development of many promising immunologic and targeted therapies for the treatment of relapsed/refractory HL. Despite these innovations, curative treatment of patients under the age of 75 with relapsed/refractory HL with good performance status remains high-dose chemotherapy followed by...
ASCT. In the future, as we refine our prognostic tools and our ability to target therapy to biology, these agents or novel combinations will be integrated into earlier lines of therapy and may provide a bridge to successful SCT for greater numbers of patients, increase survival for patients relapsed post-SCT, or potentially replace SCT as a second-line salvage approach. Yet as these drugs move into earlier lines of therapy, many important questions remain unanswered with respect to both durability and long-term toxicity. What are the short- and long-term toxicities with immunotherapy, and will they be different in earlier lines of therapy for patients with more intact immune systems? If these agents are integrated into earlier lines of therapy, how will this change the options available for patients who subsequently relapse? Will checkpoint blockade combinations result in durable remission and at any point supplant SCT as second-line salvage? Ongoing and future investigations will hopefully answer these questions and, as more exciting therapies move from bench to bedside, offer a promise of increased cure with reduced toxicity for all patients with relapsed/refractory HL.

References


HEMATOLOGIC MALIGNANCIES—PLASMA CELL DYSCRASIA
Bones in Multiple Myeloma: Imaging and Therapy
Elena Zamagni, MD, Michele Cavo, MD, Bita Fakhri, MD, Ravi Vij, MD, MBA, and David Roodman, MD, PhD

OVERVIEW

Bone disease is the most frequent disease-defining clinical feature of multiple myeloma (MM), with 90% of patients developing bone lesions over the course of their disease. For this reason, imaging plays a major role in the management of disease in patients with MM. Although conventional radiography has traditionally been the standard of care, its low sensitivity in detecting osteolytic lesions has called for more advanced imaging modalities. In this review, we discuss the advantages, indications, and applications of whole-body low-dose CT (WBLDCT), ¹⁸F-fluorodeoxyglucose (FDG)-PET/CT, MRI, and other novel imaging modalities in the management of disease in patients with plasma cell dyscrasias. We also review the state of the art in treatment of MM bone disease (MMBD) and the role of bisphosphonates and denosumab, a monoclonal antibody that binds and blocks the activity of receptor activator of nuclear factor-kappa B ligand (RANKL), which was recently approved by the U.S. Food and Drug Administration for MMBD.

Bone disease is the most frequent feature of MM, occurring in approximately two-thirds of the patients at diagnosis and in nearly all of the patients during the course of their disease.¹ Despite remarkable advances in MM therapy over the last decade, the consequences of skeletal involvement still remain clinically relevant.

Moving Beyond the Skeletal Survey

Although conventional radiography has historically been the standard of care for many years, it has several limitations. For a lytic lesion to become apparent, it requires losing more than 30% of trabecular bone. Other limitations include the prolonged study time, the difficulty to assess certain areas, such as the pelvis and the spine, the difficulty to distinguish benign osteoporosis from MM-related lesions, and the limitation in the assessment of response to antmyeloma treatment as a result of the lack of bone healing after therapy. Recently, two retrospective trials on a large number of patients with suspected SMM studied with skeletal survey and either PET/CT³ or WBLDCT⁴ demonstrated that the use of conventional radiography would have underestimated the presence of an active disease in approximately 25% to 40% of the cases. These limitations warrant investigating more advanced imaging modalities.

Whole-Body Low-Dose CT

The development of novel imaging methods has led to the substitution of whole-body x-ray (WBXR) by more advanced techniques for the identification of lytic bone lesions. WBLDCT was introduced to allow the detection of osteolytic lesions in the whole skeleton with high accuracy, no need for contrast agents, and low radiation dose (two- to threefold lower radiation dose vs. conventional CT).⁵,⁶ In several studies, WBLDCT was found to be superior to WBXR for the detection of osteolytic lesions, as evidenced by higher sensitivity and increased detection rate, resulting in greater accuracy.⁵,⁷

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Disclosures of potential conflicts of interest provided by the authors are available with the online article at asco.org/edbook.

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PET/CT
PET/CT, usually with FDG as radiopharmaceutical, can be used for staging or restaging of the disease. Several studies have reported a sensitivity and specificity between 80% and 100% for the detection of bone lesions.8,12 The combination of functional imaging with PET and the morphologic assessment with CT makes this technique the most accurate imaging modality in identifying sites of extramedullary disease,13 which has been associated with shorter progression-free survival and overall survival (OS).14 In addition, the number and metabolism of focal lesions (FLs) prior to treatment have been validated as independent prognostic factors in several prospective and retrospective studies in patients eligible for autologous stem cell transplantation (ASCT) or allogeneic stem cell transplantation.5,12,15 The presence of more than three FDG-avid FLs is known to be an independent variable associated with inferior OS and event-free survival.8 Additional prognostic information provided by PET/CT includes the level of FDG uptake quantified as maximum standardized uptake value.

Considering the ability of FDG-PET/CT to distinguish between active and inactive (e.g., fibrotic) disease, it is an excellent imaging tool to assess tumor metabolic activity and monitor response to treatment. Several studies have demonstrated a negative prognostic role for PET-positive lesions after the completion of therapy.8,9,12 Regarding minimal residual disease (MRD) evaluation, FDG-PET/CT negativity after ASCT predicted a lower risk of progression or death in patients with conventionally defined complete remission compared with patients with metabolically active sites of the disease.14 The coupling of PET/CT with different methods of MRD testing in bone marrow allows defining a more accurate (e.g., more or less) depth of response to therapy,16 which could be complementary to MRD detection tools in the bone marrow. Based on these results, FDG-PET/CT is actually considered the preferred imaging technique for evaluating and monitoring metabolic response to therapy.17 However, it is important to emphasize that both false-negative and false-positive results may occur with the use of FDG-PET/CT. In particular, false-negative scans can be related to hyperglycemia or recent administration of high-dose steroids, leading to a transient metabolic suppression. Moreover, it has been reported that in a variable rate of patients, ranging from 10% to 15%, plasma cells may not be 18F-FDG avid.18

MRI
MRI has been established as a valuable technique for the diagnosis of bone involvement in MM. MRI detects bone marrow infiltration by myeloma cells, whereas WBXR and CT detect osseous destruction. Conventional MRI protocols for MM include T1-weighted, T2-weighted with fat suppression in opposed-phase imaging, and contrast-enhanced T1-weighted sequences. Five MRI patterns of marrow involvement have been recognized in MM: normal, focal, diffuse, combined focal and diffuse, and variegated or “salt and pepper.”19,20 The field of view can be axial (spine and pelvis) or whole body. Several studies have shown that MRI, both axial or whole body, is more sensitive compared with WBXR for the detection of bone involvement in MM, with higher diagnostic precision.21,22 Studies that have compared MRI with PET/CT have shown that the two techniques are equally effective in detecting FLs.9 Studies that have compared MRI with WBLDCT have indicated an excellent agreement in terms of lesion detection, pattern, and bone marrow involvement.23 Because of its high sensitivity in revealing bone marrow involvement, MRI is now used for the discrimination between SMM and active MM. Several studies have shown that approximately 40% to 50% of patients with normal WBXR had abnormal findings on MRI examinations. Two studies showed that patients with SMM with more than one FL on MRI had a median time to progression of symptomatic disease of 13 to 15 months and a 2-year probability of progression of approximately 70% to 80%.24,25 In both studies, the presence of more than one FL on MRI was an independent adverse prognostic factor for progression to active disease. Regardless of MRI findings at initial diagnosis, the progression of FLs on MRI during the follow-up of patients has been associated with progression of SMM to MM.26 FLs detected on MRI correlate with standard prognostic factors, in particular cytogenetics and clinical outcomes.22,27,28 On the contrary, the prognostic meaning of the diffuse pattern is less clear; in this regard, the addition of the diffusion-weighted imaging (DWI) technique, which derives its contrast mainly from differences in the diffusivity of water molecules in the tissue environment, may be an adjunct tool to clarify this issue.29

Changes in MRI patterns may be associated with response to therapy and used to gauge the effects of antimyeloma

PRACTICAL APPLICATIONS
- The low sensitivity of skeletal survey in identifying lytic bone lesions in patients with MM has necessitated the use of more sophisticated imaging modalities, such as WBLDCT, WBMRI, and FDG-PET/CT.
- In 2014, the IMWG updated the definition of MM, by incorporating novel criteria in the definition of MM-defining bone lesions, including the presence of at least one lytic lesion detected by skeletal radiography, CT, or FDG-PET/CT or the presence of more than one focal lesion on MRI studies.
- The European Myeloma Network and the European Society for Medical Oncology guidelines have recommended WBLDCT as the imaging modality of choice for the initial assessment of MM-related lytic bone lesions.
- MRI is the gold-standard imaging modality for detection of bone marrow involvement and the preferred imaging technique to rule out spinal cord compression in patients with MM, whereas PET/CT provides valuable prognostic data and aids in assessment of response to therapy.
- Bisphosphonates and denosumab, a monoclonal antibody that binds and blocks the activity of RANKL, are approved for the management of MMBD.
treatment.32,30 However, standard protocols for MRI are not allowing a clear definition of response and may often lead to false-negative results.

Future Steps and Open Issues
Despite major advances in imaging modalities used in MM, a wide range of issues must be further investigated. The standardization of PET/CT is currently ongoing.31 In addition to 18F-FDG, new PET/CT tracers targeting different metabolic pathways or receptors expressed by MM cells, acting as potentially more sensitive molecular imaging biomarkers, have been preliminarily investigated in limited series of patients with MM. However, their lower availability, the lack of direct comparisons with 18F-FDG, and the interpatient tumor heterogeneity regarding specific targets preclude any definitive conclusion.32-35 MRI functional approaches—such as dynamic contrast enhanced, which quantifies perfusion, and DWI, which enables quantitative assessment of disease burden through measuring the apparent diffusion coefficient, influenced by tissue microarchitecture and marrow cellularity—seem promising tools to evaluate the disease after therapy.36-38 Initial experience with DWI whole-body MRI (WBMRI) on several independent small series of patients have shown a high sensitivity associated with this technique. DWI WBMRI is a particularly powerful imaging tool in detecting diffuse marrow disease, and evaluating early response to therapy through noteworthy changes in apparent diffusion coefficient in patients on therapy39,40 and in remission after the end of treatment.41-43 However, published studies were mainly based on retrospective analyses of heterogeneous patients, and no standardization in the interpretation of the results is currently available. Prospective comparison of DWI MRI with PET/CT, both prior to and after treatment, are needed to optimize the use of imaging for prognosis and for evaluation of metabolic response to therapy.44 Moreover, it is important to establish the relationship between complete metabolic response and MRD negativity at the bone marrow level, as well as to define the impact of MRD assessment on treatment strategies. Upcoming prospective trials, extensively applying novel techniques evaluating MRD both inside and outside the bone marrow, will help address these issues and define the role of these promising tools in clinical practice.

PRACTICAL USE OF IMAGING FROM MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE TO MULTIPLE MYELOMA

Multiple Myeloma
There is considerable heterogeneity in clinical practice regarding the incorporation of the different imaging modalities in the management of disease in patients with plasma cell dyscrasias. The International Myeloma Working Group (IMWG) has published consensus statements on the use of MRI and FDG-PET/CT in the management of disease in patients with MM17,19 (Sidebar 1; Tables 1 and 2). The European Myeloma Network and the European Society for Medical Oncology have also published guidelines on the use of imaging in patients with MM.45,46

Use of imaging at diagnosis. MM has historically been defined as clonal bone marrow plasma cells 10% or more or biopsy-proven bone or extramedullary plasmacytoma along with meeting one or more MM-defining clinical features, referred to as CRAB criteria (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions).47 The European Myeloma Network guidelines46 and European Society for Medical Oncology guidelines45 have recommended WBLDCT as the imaging modality of choice for the initial assessment of MM-related lytic bone lesions. If the physician has access to WBLDCT scanning and is reimbursed by insurance, WBLDCT would be our preferred imaging modality for initial screening to evaluate presence or absence of lytic lesions. If WBLDCT scanning is not available, performing a skeletal survey (WBXR) for the initial evaluation of all patients with newly diagnosed MM (NDMM) is recommended.

In 2014, the IMWG updated the definition of MM, refining the role of imaging in the identification of bone lesions as a MM-defining event.48 The novel criteria include in the definition of bone lesions: (1) the presence of at least one lytic lesion detected not only by conventional radiography but also by one of the novel morphologic imaging techniques, such as CT, WBLDCT, or PET/CT; and (2) the presence of more than one FL on MRI. This update was introduced after the clear demonstration that the novel imaging techniques have a higher detection rate as compared with skeletal survey.49

According to the IMWG consensus statement, PET/CT scan at the time of diagnosis provides helpful prognostic data that can inform treatment decisions (grade A).17 Several
experts now recommend routine use of PET/CT in place of skeletal surveys because of the additional prognostic value it provides at diagnosis. However, this practice has not yet been universally endorsed. In our own practice, if a skeletal survey indicates the presence of osteolytic lesions, we do not routinely perform a PET/CT scan, but would proceed with a PET/CT in patients with no lesions visible on skeletal survey or in patients who have nonsecretory or oligosecretory disease.

**Use of imaging in assessing response to therapy.** Conventional radiography cannot be used for therapy monitoring because even in the presence of response to therapy, osteolytic lesions rarely show radiographically identifiable changes. However, multiple retrospective and prospective studies have established the importance of PET/CT to evaluate response to treatment of patients with MM. Changes in FDG uptake on PET/CT provide an earlier evaluation of response compared with MRI.

The IMWG consensus statement endorses PET/CT as the preferred imaging modality to evaluate and monitor metabolic response to therapy in patients with MM (grade A). PET/CT negativity before ASCT is associated with favorable post-ASCT outcomes (grade B). For patients with conventional ASCT-ineligible and patients with RRMM must be designed, independent studies have designated a negative prognostic value for the presence of EMD and the presence of more than three FLs, specifically following upfront ASCT. The prognostic value of SUV_max may benefit from additional treatment or a change in therapy. For this reason, we still do not use PET/CT scans routinely to monitor response to therapy, except in patients with oligosecretory or nonsecretory disease.

**Use of imaging at disease progression.** In patients with new bony pain or clinical suspicion for a new lytic lesion, a skeletal survey would be warranted. There are no established guidelines for the use of PET/CT scan at the time of disease progression.

### TABLE 1. Summary of IMWG Consensus Statements Regarding the Use of MRI in Plasma Cell Dyscrasias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>MGUS</td>
<td>MRI is not recommended as part of initial evaluation in patients with MGUS unless there are clinical symptoms, physical examination findings, or laboratory abnormalities that increase suspicion for active disease.</td>
</tr>
<tr>
<td>Solitary plasmacytoma</td>
<td>MRI should be included in initial evaluation of patients with solitary bone plasmacytoma to better examine the extent of the disease and exclude other possible lesions (grade A).</td>
</tr>
<tr>
<td>SMM</td>
<td>Patients with one definitive FL should be classified as symptomatic MM that requires therapy (grade A). If MRI is unavailable, PET/CT is recommended as part of the initial workup of patients with a suspicion of extramedullary plasmacytoma or solitary bone plasmacytoma to rule out the presence of additional sites of disease (grade A). Patients who meet the criteria for MM but have ≥1 FL with osteolytic changes with increased uptake on PET/CT should be reclassified as having MM rather than SMM (grade A).</td>
</tr>
<tr>
<td>MM</td>
<td>MRI is the gold-standard imaging modality for detection of bone marrow involvement in MM (grade A). MRI is recommended to distinguish between SMM and active MM (grade A). At diagnosis: Considering the higher sensitivity in detecting lytic bone lesions, the incorporation of new imaging modalities (WBLDCT and PET/CT) for accurate diagnostic purposes is recommended (grade A). For prognosis: PET/CT at the time of diagnosis will provide invaluable prognostic data that can inform treatment decisions (grade A). Although more studies for ASCT-ineligible and patients with RRMM must be designed, independent studies have designated a negative prognostic value for the presence of EMD and the presence of more than three FLs, specifically following upfront ASCT. The prognostic value of SUV_max should be further investigated (grade C). MRI is recommended for treatment follow-up.</td>
</tr>
</tbody>
</table>

Abbreviations: IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; FL, focal lesion; WBMRI, whole-body MRI; EMD, extramedullary disease.

### TABLE 2. A Summary of IMWG Consensus Statements Regarding the Use of PET/CT in Plasma Cell Dyscrasias

<table>
<thead>
<tr>
<th>Disease</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGUS</td>
<td>No consensus statement has been issued.</td>
</tr>
<tr>
<td>Solitary plasmacytoma</td>
<td>If MRI is unavailable, PET/CT is recommended as part of the initial workup of patients with a suspicion of extramedullary plasmacytoma or solitary bone plasmacytoma to rule out the presence of additional sites of disease (grade A).</td>
</tr>
<tr>
<td>SMM</td>
<td>If WBMRI is negative, and MRI is unavailable, PET/CT is recommended to distinguish between SMM and active MM (grade A). Patients who meet the criteria for SMM but have ≥1 FL with osteolytic changes with increased uptake on PET/CT should be reclassified as having MM rather than SMM (grade A).</td>
</tr>
<tr>
<td>MM</td>
<td>At diagnosis: Considering the higher sensitivity in detecting lytic bone lesions, the incorporation of new imaging modalities (WBLDCT and PET/CT) for accurate diagnostic purposes is recommended (grade A). For prognosis: PET/CT at the time of diagnosis will provide invaluable prognostic data that can inform treatment decisions (grade A). Although more studies for ASCT-ineligible and patients with RRMM must be designed, independent studies have designated a negative prognostic value for the presence of EMD and the presence of more than three FLs, specifically following upfront ASCT. The prognostic value of SUV_max should be further investigated (grade C). MRI is recommended for treatment follow-up.</td>
</tr>
</tbody>
</table>

Abbreviations: IMWG, International Myeloma Working Group; RRMM, relapsed and/or refractory MM; EMD, extramedullary disease; SUV_max, maximum standardized uptake value.
progression after first-line therapy. However, if patients who are on maintenance therapy or are being observed expectantly after frontline therapy develop biochemical evidence of disease progression (defined as 25% or more increase in the serum or urine M-protein or 25% or more difference between involved and uninvolved serum free light chains from its baseline or the development of new plasmacytomas or hypercalcemia\textsuperscript{52-54}) but have no new lesions on skeletal survey, we perform a PET/CT scan to assess the disease status. In patients who have change (or reinstate) therapy with a three-drug regimen employing either daratumumab or carfilzomib. In patients who do not have FDG-avid lesions, we often adjust the dose of the drugs being used in maintenance or treat patients with an elotuzumab-based three-drug regimen. For patients with new CRAB criteria (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions) or symptomatic progression, we are more likely to use a daratumumab- or carfilzomib-based three-drug regimen.

With continued improvement in the OS of patients with MM, a growing number of patients with a serum M-protein of elevated serum free light chain level at diagnosis develop a nonsecretory or oligosecretory phenotype at time of elevated serum free light chain level at diagnosis of MM, a growing number of patients with a serum M-protein of elevated serum free light chain level at diagnosis develop a nonsecretory or oligosecretory phenotype at time of elevated serum free light chain level at diagnosis of MM. For patients with high-risk features (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions) or symptomatic progression, we are more likely to use a daratumumab- or carfilzomib-based three-drug regimen.

Smoldering Multiple Myeloma

As in MM, all patients with a diagnosis of SMM should initially be evaluated by WBXR. Based on the IMWG consensus statement, if WBXR is negative, and MRI is available, patients with SMM should undergo WBMRI (or MRI of the spine and pelvis if WBMRI is not available). Patients with one unequivocal FL on MRI (diameter of 5 mm) should be considered to have symptomatic MM requiring therapy (grade B). Patients with equivocal FLs should undergo a repeat MRI within 3 to 6 months and, in cases of radiographic progression, should be considered as symptomatic patients who need therapy (grade C).\textsuperscript{19} If WBXR is negative, and WBMRI is unavailable, PET/CT scan is recommended to differentiate between active MM and SMM (grade A).\textsuperscript{17} The presence of one or more FLs with lytic changes and increased uptake on PET/CT scan indicates active MM and calls for initiation of treatment.\textsuperscript{17}

Multiple studies have shown that the risk of progression to MM is higher in patients with high-risk SMM,\textsuperscript{24,56,57} and these patients are candidates for clinical trials. Based on the current guidelines, from a radiographic imaging standpoint, the definition of high-risk MM includes bone marrow plasma cells 10% or more in addition to either:

- MRI with diffuse abnormalities or one FL and/or
- PET/CT with FL with increased uptake without underlying osteolytic bone destruction.\textsuperscript{58}

Solitary Plasmacytoma

Plasmacytoma is a plasma cell dyscrasia containing abnormal plasma cell clones within soft tissue (extramedullary plasmacytoma) or bone. In patients who are initially diagnosed with solitary bone plasmacytoma based on WBXR, it is important to examine the bone marrow and other sites to rule out the presence of cytologically undetectable plasma cell clones elsewhere. WBMRI should be considered as part of the initial evaluation in patients with solitary plasmacytoma to better determine the extent of the disease and exclude other occult lesions (grade A).\textsuperscript{17} If WBMRI is not available, MRI of the spine and pelvis should be considered to rule out bone marrow infiltration. PET/CT scan, as well, is a practical imaging technique to exclude additional sites of proliferating clonal plasma cells (grade A).\textsuperscript{17}

Monoclonal Gammopathy of Undetermined Significance

Monoclonal gammopathy of undetermined significance (MGUS) is characterized by the absence of osteolytic lesions.\textsuperscript{48} In patients with a diagnosis of low-risk MGUS (defined as serum M-protein 1.5 g/dL or less, immunoglobulin G isotype, and normal free light chain ratio\textsuperscript{59}), a skeletal survey can be deferred. Patients with MGUS with high-risk features should undergo WBXR to rule out the presence of lytic lesions. To date, MRI or PET/CT scan has not been deemed necessary as part of the routine initial workup of patients with MGUS,\textsuperscript{17,60} unless there are clinical symptoms, physical examination findings, or laboratory abnormalities that increase suspicion for active disease.

Optimal Use of Bisphosphonates and Other Agents in Bone Disease in Multiple Myeloma

MM is the most frequent cancer that involves the skeleton, with 90% of patients developing bone lesions over the course of their disease.\textsuperscript{61} Bone involvement is responsible for the most devastating consequences of MM, including pathologic fractures that can occur in 50% to 60% of patients, debilitating pain,\textsuperscript{62} and increased mortality risk by up to 20% in patients with MM.\textsuperscript{63} In addition, MMBD can cause hypercalcemia (15%),\textsuperscript{64} and spinal cord compression syndromes (5%),\textsuperscript{65} impacting both quality of life and survival of patients. MMBD is characterized by purely lytic bone lesions due to increased local osteoclast activity adjacent to MM cells that is accompanied by severely suppressed osteoblast activity.\textsuperscript{66} This uncoupling of the normal bone remodeling process, by which increased osteoclast activity is coupled to new bone formation at the sites of previous bone removal, results in little or no new bone formation despite increased bone resorption.\textsuperscript{67} Moreover, the majority of bone lesions induced by MM do not heal, even when the patients are in complete remission, as a result of the persistent suppression of osteoblast activity.\textsuperscript{68}

Bisphosphonates

Treatment of MMBD requires control of tumor proliferation, increased bone destruction, and, if possible, reversal
of the persistent suppression of bone formation. Current bone-targeted therapies focus on blocking osteoclast activity because safe, effective bone anabolic agents are still not available clinically. Bisphosphonates and denosumab (discussed below) are approved for the management of MMBD. Pamidronate, zoledronic acid, and clodronate are the most commonly used bisphosphonates. Bisphosphonates approved for treating myeloma in the United States are zoledronic acid given at 4 mg intravenously over 15 to 30 minutes and pamidronate given at 90 mg intravenously over 120 minutes every 3 to 4 weeks. Zoledronate and pamidronate are equally efficacious for treating MMBD. All of these agents decrease osteoclast activity and reduce development of new osteolytic lesions, pathologic fractures, and hypercalcemia in patients with MM. Bisphosphonate treatment also improves bone pain through inhibition of osteoclast-mediated proton release. However, bisphosphonate treatment only decreases skeletal-related events (SREs; pathologic fractures, spinal cord compression, or the necessity for surgery or radiation to bone) by 50%. Further, uncommon but major complications associated with bisphosphonate therapy occur and include renal insufficiency and osteonecrosis of the jaw (ONJ). Because of these complications, serum creatinine should be monitored before each dose. If patients have mild to moderate renal impairment (estimated creatinine clearance of 30 to 60 mL/min), the dosage of zoledronate should be decreased according to the package insert. Zoledronate should not be used in patients with severe renal impairment. If the creatinine clearance is less than 30 mL/min, 90 mg of pamidronate can be infused over 4 to 6 hours. All patients receiving bisphosphonate therapy should have a comprehensive dental examination and necessary dental treatments prior to starting bisphosphonate therapy and maintain excellent oral hygiene, have regular dental evaluations, and avoid invasive dental procedures.

Although bisphosphonates are very effective for preventing SREs, major questions about bisphosphonate therapy have centered on when to initiate treatment in patients with MM, how frequently to treat patients, and the duration of treatment. Prior to the MRC IX trial, only patients with active myeloma and lytic bone disease on imaging studies were treated with bisphosphonates. The MRC IX trial compared the effects of the addition of zoledronate or clodronate (a less potent oral bisphosphonate not approved in the United States) to two treatment regimens in 1,960 newly diagnosed patients with MM. All patients received bisphosphonates, regardless if bone lesions were detectable on skeletal surveys. Results from the MRC IX trial showed a noteworthy increase in progression-free survival and OS for all patients receiving zoledronate compared with clodronate, with an increase in OS of 5.5 months, regardless if they had detectable bone lesions. Importantly, patients without detectable bone lesions also had reduced occurrence of SREs at relapse. These findings resulted in the ASCO guidelines for starting bisphosphonate therapy in any newly diagnosed patient who is on treatment for active myeloma.

Because the incidence of ONJ is related to duration of bisphosphonate treatment more than 2 years, tooth extraction, and surgery to the jaw and is more frequent with zoledronate-based regimens, several studies have assessed if the dosing interval for zoledronate could be extended from monthly to every 3 months and still maintain its efficacy. The Z-Mark study examined the efficacy of 3-month zoledronate therapy in patients who had received 1 to 2 years of monthly zoledronate therapy and had urinary N-telopeptide of type I collagen levels of less than 50 nmol/mmol creatinine. Urinary N-telopeptide of type I collagen is a bone resorption biomarker. Patients with urinary N-telopeptide of type I collagen levels greater than 50 nmol/mmol creatinine, developed an SRE on the study, or had disease progression were treated with monthly zoledronate. Seventy-nine of the 121 patients received the 3-month schedule, with only 12 patients developing an SRE over the 2 years of the study. This low SRE rate (8.9%) supported less frequent dosing of zoledronate in patients who have received 1 to 2 years of monthly treatment and have stable disease. It also is consistent with recent results that showed very low rates of SREs in patients receiving more effective modern therapies.

A more recent second larger randomized trial compared every 12-week to 4-week zoledronate therapy in a group of patients that comprised 1,544 patients with bone metastasis and 278 patients with myeloma. This study found no differences in SREs, incidence of ONJ, or renal dysfunction between the treatment groups. However, only 795 of the 1,822 patients randomly assigned initially completed the study, with a similar high dropout rate for the patients with MM and those with bone metastasis. Taken together, these studies are not definitive, but suggest that less frequent zoledronate dosing may be feasible in patients with MM with very stable disease. However, extending the dosing interval for zoledronate must still be based on the treating physician’s discretion.

Because bisphosphonates accumulate and remain in bone for years, the question remains how long patients with MM should be treated with bisphosphonates. Randomized trials of bisphosphonates in patients with cancer have only examined the effects of bisphosphonate treatment of up to 2 years. The MRC IX trial did report the results from a small number of patients who continued bisphosphonate therapy for up to 5 years. These patients showed continued benefit from prolonged bisphosphonate treatment intent on preventing SREs. However, incidence of ONJ continued to increase in these patients over the same time period. Thus, current guidelines recommend treating patients with bisphosphonates for up to 2 years and then consider stopping bisphosphonate treatment until relapse.

Denosumab
Denosumab, a monoclonal antibody that binds and blocks the activity of RANKL, was recently approved by the Food and Drug Administration for MMBD. The approval was based on the results of a large phase III trial of denosumab versus zoledronate for MMBD. The RANK/RANKL signaling
pathway is a major regulator of both normal and pathologic bone remodeling. RANKL is expressed by stromal cells, osteoblasts, and osteocytes in bone and is also secreted by activated T lymphocytes and MM cells.60,61 Multiple cytokines and hormones known to stimulate bone resorption (e.g., parathyroid hormone, 1,25-OH2VitD3, prostaglandins, interleukin-1β, and tumor necrosis factor-α) increase RANKL expression by osteoblasts.63–67 RANKL binds its receptor RANK on the surface of osteoclast precursors and mature osteoclasts and stimulates a number of signaling cascades vital for osteoclast differentiation, survival, and activity.88,89 In the recently completed trial, denosumab was found to be noninferior in delaying first on study SRE compared with zoledronic acid, and OS was similar between the two treatment groups. Importantly, an exploratory endpoint, median progression-free survival, showed that progression-free survival was increased by 10.7 months for patients receiving denosumab compared with those receiving zoledronate. Hypocalcemia occurred more frequently in the denosumab arm, consistent with its known safety profile, but ONJ rates were similar. Thus, denosumab represents a newly approved antiresorptive therapy for patients with MM. Similar dental monitoring and vitamin D and calcium supplementation must be used for patients receiving denosumab as for patients receiving bisphosphonates. As noted above, current treatments for MMBD, bisphosphonates and denosumab, primarily target bone destruction by osteoclasts and do not increase bone formation. Several potential bone anabolic agents are in preclinical or clinical trial for MMBD that may be available in the near future to repair or prevent bone lesions and their terrible sequelae in patients with MM.

References


Value and Cost of Myeloma Therapy—We Can Afford It

Rafael Fonseca, MD, and Jennifer Hinkel, MS

OVERVIEW

A national conversation regarding the price and affordability of drugs exists, where concern for value and benefits of medications is challenged by the increasing price of both injectable and oral medications, including the cost of care of myeloma. At the same time, we have seen unprecedented improvements in the overall survival of patients with myeloma, mostly because of the availability of these new drugs. Here, we present data to assert that these medications and associated expenses are of direct benefit to patients and society. The entrepreneurial reward for drug development in the United States has fueled vigorous drug development efforts that have culminated in the approval of 11 new drugs for the treatment of myeloma by the U.S. Food and Drug Administration (FDA) since 1999. These patented drugs are available to patients in the United States usually at a higher price than in the rest of the world. Nevertheless, the majority of patients, via direct copay assistance or through indirect support via third parties, have access to these drugs irrespective of their socioeconomic status. One of the major regulatory hurdles that prevents access to these drugs is the legal impossibility that pharmaceutical companies have in directly supporting copay assistance for patients with government-funded health care. Moreover, assessments of value should include formal pharmacoeconomic analyses performed by experts. Interference with market forces and coercive action, such as price controls, or exercising eminent domain in the quest for cheaper medications will stymie innovation and rob us of the cures of the future.

The prognosis for patients with myeloma has improved over the last 15 years, primarily because of the advent of novel therapeutics. Myeloma is a disease model for drug development, where an array of collaborative efforts between academic centers and the pharmaceutical companies have led to the approval of 11 new medications since 1998 (Fig. 1). Before these approvals, myeloma was treated with melphalan, corticosteroids, and older chemotherapy agents. In 1993, the median survival of patients with myeloma was approximately 2 years (29 months), with rare long-term survivors (Fig. 1). Today, it is estimated that the average patient with myeloma will live over 8 years from the time of diagnosis (perhaps longer), and a measurable fraction of patients can be cured. The pace of progress is so fast that increments in these survival changes can be documented over short periods of time. However, the fight against this disease is not complete. Treatments can be lengthy, be associated with toxicity, and have the cost associated with chronicity of therapy, and most patients ultimately succumb to their disease. The search for better, faster, less toxic, and affordable treatments must continue.

Much progress has occurred over the last 100 years in the quest for medical improvements. Through a combination of scientific advances, public health initiatives, the economic betterment of populations, and serendipity, the average lifespan of humans has increased by about 30 years over that same period. The scourges of the past are no more; vaccinations have eradicated polio, antimicrobials have greatly reduced the risk of infectious diseases, and improvements in the prevention and management of cardiovascular health have greatly improved the human experience. Among others, two major threats still must be overcome: cancer and neurodegenerative disorders. The challenge in finding solutions for diseases, like Alzheimer disease, is daunting, so much so that various pharmaceutical companies (e.g., Pfizer) have explicitly stated that they will no longer engage in research efforts for that terrible disease. That is not the case in cancer. Progress is being made on a constant basis: sometimes incrementally and sometimes exponentially. It is not inconceivable to envision a future where the majority of cancer cases can be controlled or cured. We hope for a future that looks back at 2018 and sees with incredulity the existence of cancer centers (as we do for tuberculosis sanatoriums). Moreover, myeloma is a prime example of how progress has happened, but the totality of answers is not there yet.

In this article and its accompanying session presented at the 2018 ASCO Annual Meeting, we intend to discuss whether this progress comes forward as a reasonable value proposition for patients and society. This paper will primarily address value associated with patented and branded medication. Although most prescription medications are generic (more than 90%), the key elements in the treatment...
of myeloma still have patent exclusivity. In the case of generic (and perhaps biosimilar medications?) medications, competitive forces should quickly drive prices down, an important step in the lifecycle of drugs. However, market distortions have allowed lack of competition to prevent downward pricing, and even in some cases, we have seen dramatic increases (e.g., daraprim). Medications central to the treatment of myeloma, such as melphalan and cyclophosphamide, have greatly increased in price. Recent actions by the U.S. Food and Drug Administration have focused on the rapid approval of generic medications, and hopefully, this, in time, will allow a more competitive landscape that will make these medications better priced.

BACKGROUND FOR THE CURRENT CONCERN OF DRUG PRICES

“Skyrocketing” Prices

The rapid rise in the price of medications is a commonly cited concern; this argument goes hand in hand with discussing increasing health care costs in general and the financial pressures exerted on the health care system and individual patients. However, is it truly the case that drug costs are “skyrocketing”? Drugs compose only a small fraction of the total costs of health care: 10% at large and 20% by some estimates for cancer care. Cancer drugs constitute only about 1% of total health care costs. Two recent analyses show that the actual increase in prices, after discounts and rebates are applied, is much lower than what intuitively would be anticipated. Popovian4 shows that “in December 2017, the Centers for Medicaid and Medicare Services released National Health Expenditure data for 2016. The drug expenditure’s increased by 4.3%.”4 Express Scripts, one of the nation’s largest Pharmacy Benefit Managers, just reported that, in 2017, drug spending rose by only 1.5%, and that same year, the rise in specialty drugs was the lowest that they had recently recorded.5 Overall, drug spending is not skyrocketing.

Do We Get the Value for These Drugs?

There is no mutually agreed on way to estimate value for medications. Health economics experts have used metrics, such as the cost per quality-adjusted life-year, to estimate a value of medical interventions. Such metrics are fraught with problems in that they likely underestimate the value of a person’s life after a cancer diagnosis; the cost per quality-adjusted life-year metric has met criticism from health economists, bioethicists, patient advocates, and physicians, pointing out methodologic and ethical flaws.6 In some cases, patients and physicians advocating against this metric state that time becomes more valuable for patients after the stark reminder of human mortality that accompanies a cancer diagnosis.7 Other metrics of value have no direct economic evaluation, such as reaching a landmark life event (“value of landmark survival”; e.g., a wedding), improving quality of life, lessening of toxicity, or other imponderable benefits. One recent addition to this list includes what has been called the “value of options”; this term refers to the capacity that a patient has to live long enough to be able to realize the benefit of future therapy, a therapy still in development. Myeloma is a shining example of how clinical trials bring forward new options for patients. Patients with myeloma who have now lived long enough to see the possibility of participating in a chimeric antigen receptor (CAR) T cell trial can do so because of the extended survival offered to them by these novel treatments.

Cost-Effectiveness Studies

Numerous studies have evaluated the cost-effectiveness of myeloma treatments. Table 1 provides a summary of recent pharmacoeconomic studies that include novel myeloma agents.8–15 Although numerous studies exist (searched via the combination of “cost-effectiveness” and “real world” alongside “myeloma”), many have done comparisons of older drugs and regimens no longer relevant in the clinic. Although some of the studies go beyond the willingness to pay of $150,000 per quality-adjusted life year (QALY) threshold, several studies show favorable results, even for daratumumab combinations.12 Other studies have looked at monotherapy drugs with cost-effectiveness ratios that are similar for pomalidomide, daratumumab, and carfilzomib.16 These analyses have been conducted in partnership with experts in the field of myeloma who can attest to the clinical soundness of the regimens being tested. Importantly, these analyses have been done in partnerships with health economists who can professionally establish parameters and framework for these studies, a set of skills not commonly possessed by physicians.

Aguiar et al reported on the quality of pharmacoeconomic studies for myeloma using the Consolidated Health Economic

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PRACTICAL APPLICATIONS

- Novel therapeutics have greatly improved the outcomes of patients with myeloma and provide value.
- Absent formal pharmacoeconomic analysis, it is impossible to gauge economic value of drugs to both individual patients and society at large.
- Although there are legitimate concerns about the cost of drugs and particularly, the impact of patient out-of-pocket costs, the dialogue can only advance in the setting of rigorous academic objectivity and with an eye to pragmatic solutions that benefit patients first and foremost.
- The future of myeloma is bright and mostly so because of the availability of new therapeutics.
- Aspirations of societal responsibility in terms of achieving lower health care costs via price controls or similar mechanisms are at odds with the primary responsibility of the physician: the patient.
Evaluation Reporting Standards (CHEERS) and identified 132 potentially relevant studies, eight of which met their inclusion criteria. They concluded that although better quality reporting is needed, the majority of included studies reported favorable cost-effectiveness ratios. Although there are challenges associated with comparing U.S.-based and European cost-effectiveness studies, many studies conducted in Europe have also shown that novel myeloma agents are cost-effective. For example, Borg et al estimated ICER of €62,000 for pomalidomide as an add-on to best supportive care in Sweden. Blommestein et al showed that most novel agents are cost-effective at incremental cost levels of €24,000 to €34,000. One recent study attempted to use value-based frameworks and found that they are not yet developed in such way that they can help guide therapy, and a more recent analysis has shown that value-based frameworks suffer from the lack of consideration of patient heterogeneity, for instance in myeloma risk stratification.

**Limitations of Cost-Effectiveness Studies**

It is critical to recognize that cost-effectiveness modeling depends on assumptions and input variables such that modifications in the parameters used can have a significant impact on the results (e.g., survival hazard ratios, treatment
duration, time horizon, heterogeneity considerations, real drug costs that are difficult to obtain). For example, prior published analyses have not included manufacturer rebates, which can be substantial. Another major consideration is whether using a QALY discount in these models is ethical and fair; why not use life years alone? One current problem is that modeling studies omit inclusion of measurable value associated with cost. To this effect, Lakdawalla et al proposed a quality-adjusted cost of care, a new metric that incorporates both health care spending and health improvement. They found that novel myeloma therapies increased the treatment cost from $36,607 in 2004 to $109,544 in 2009. However, this was offset by $67,900 in health benefits.

Real-World Data
We have recently reported that the cost of caring for myeloma has increased over the last several years, but several other factors contribute to this increase, particularly nondrug outpatient expenses. In 2000, the total all-cause health care cost of myeloma was $3,263 per patient per month (PPPM; $346 PPPM or 10.6% for myeloma treatment–related drug costs), and increased to $14,656 PPPM in 2014 ($4,176 PPPM or 28.5% for myeloma treatment–related drug costs). When only looking at patients with newly diagnosed myeloma who received treatment within a year of diagnosis, the total all-cause health care cost increased to $18,424 PPPM in 2014. The estimated $4,176 PPPM is the average cost of drugs divided by the length of follow-up for patients, including months when they are not on therapy. Arikian et al reported similar estimates also using claims data, including 2,843 newly diagnosed and 1,361 relapsing myeloma patients. In first-line therapy, the total monthly cost for patients with newly diagnosed myeloma declined from $15,734 initially to $5,082 at 18 months, whereas second-line therapy monthly costs rose to $13,876 in the first 3 months but declined to $6,446 at 18 months after treatment initiation.

Myeloma Considerations
Two very important considerations are worth noting when discussing the cost of care of myeloma. First, myeloma is an

<table>
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<tr>
<th>ICER Studies</th>
<th>Control</th>
<th>Regimen Line</th>
<th>LY Time</th>
<th>Cost ($)</th>
<th>QALY Time</th>
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<td>Jakubowiak et al</td>
<td>Vd</td>
<td>KRd</td>
<td>1–3 prior</td>
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<td>VMP</td>
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<td>Rd</td>
<td>Daratumumab-Rd</td>
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<td>7.38</td>
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<td>All (29); First</td>
<td>14,656; 18,424</td>
<td></td>
</tr>
<tr>
<td>MacEwan et al</td>
<td>All costs</td>
<td>22,527</td>
<td></td>
</tr>
<tr>
<td>Chen et al</td>
<td>All</td>
<td>18,298</td>
<td>102,000</td>
</tr>
</tbody>
</table>

Note: MacEwan et al: PPPM costs are only for the months under active treatment and do not include rebates. Fonseca et al: PPPM costs are over the lifetime of the patient. Arikian et al: PPPM costs are for the duration of therapy and until the next line.

Abbreviations: ZA, zoledronic acid; Rd, lenalidomide plus dexamethasone; LY, life years; QALY, quality-adjusted life-year; ICER, incremental cost-effectiveness ratio; K, carfilzomib; VMP, bortezomib, melphalan and prednisone; NA, not applicable; Kd, carfilzomib plus dexamethasone; Pd, pomalidomide plus dexamethasone; Vd, bortezomib plus dexamethasone; PPPM, per patient per month.
outlier as a disease where we have been very fortunate to have a large number of FDA approvals, and, although new treatment allows for better disease control, they also stress payers’ budgets. This is not the case for all malignancies. We should not penalize success. The second consideration is that treatments are not always given in optimal ways (e.g., fewer patients receive the best treatment than they should) and often treatment is only given for a short period. Qian et al showed that among 9,617 myeloma patients, only 3,735 (38.8%) used bone-protecting agents, a standard of care for myeloma.26 MacEwan et al showed that the average duration of treatment by line of therapy was 7 months for the first line, 6 months for the second line, and 5 months for the third line.12 There is also a very high level of attrition among the various lines of therapy, because of some reasons, including the inability to control the disease or death, leading to total decreased utilization of drugs. The realized cost of the care of myeloma is less than what it would be if optimal therapy were employed.

What about other analyses that find a low or questionable value to myeloma medications? Three examples will help to quickly expose their limitations. Most notable among these is the analysis done by the Institute for Clinical and Economic Research.27 The Institute for Clinical and Economic Research convened a panel to evaluate and grade value of myeloma drugs but reached clinically illogical conclusions given the lack of input from clinician experts in their modeling.28 The Institute for Clinical and Economic Research concluded that panobinostat was the best value drug for myeloma. Another academic analysis of the three immunomodulatory drugs concluded that thalidomide is probably equivalent to lenalidomide for the treatment of myeloma, with the exception of a reduced rate of peripheral neuropathy.29 Lastly, a study done at MD Anderson questions whether novel agents are cost-effective as opposed to old chemotherapy as induction therapy for myeloma, regimens that are no longer in use in clinical practice.10

What about the macroeconomic analysis of the benefit of cancer therapy? One study by Murphy and Tope30 showed that a 1% reduction in cancer mortality has a present value to current and future generations of Americans of nearly $50 trillion, and this value for a cure would be approximately $50 trillion. An economic valuation of the war on cancer was published in 2010 by Lakdawalla et al,31 and they found that the improvements in cancer survival have resulted in millions of additional life-years and trillions in social value for Americans. Specifically, the research investments during a 12-year period (from 1988 to 2000) bought 23 million additional life-years with an estimated value of $1.9 trillion.31 The total cost of care for patients during this period was estimated between $98 and $393 billion, meaning that patients realized between 82% to 95% of the total benefit.31 An important consideration for myeloma is that some cancers that affect more the elderly and thus living longer may not result in work-associated economic benefit, as much but there is still value in the domains above. Also, it should be noted that a prolonged life will result in additional health care expenditures. However, this does not diminish the value of current therapies.

**Copayments and Medical Bankruptcy**

How do drug prices affect individual patients? They do so in two ways—first by contributing to calculations that determine the cost of insurance premiums and second through cost-sharing mechanisms that are imposed by insurers at the time of purchase (copayments or coinsurance). Determinations of the insurance premium are more of an abstract consideration when patients consider coverage plans in the case of catastrophic illness, usually without the prior knowledge of specific needs.

Patients are most directly affected by out-of-pocket costs, such as copays. Because of this and the conversation surrounding drug prices, the lay media has conflated the legitimate concern of medical bankruptcy with the cost of prescription drugs. A clarification is needed. Being sick (more so with cancer) is expensive. It is expensive not only because of the cost of drugs but also because of loss of revenues (patients and caregivers cannot work in many instances) and expenses, such as travel, hospital, and doctor bills. The risk of bankruptcy doubles after a cancer diagnosis, but the net risk is quite low. In one study, Ramsey et al32 noted that the risk of bankruptcy increased from 0.7% (baseline) to 1.7% in the 5 years that follow a cancer diagnosis. Also, no study has conclusively linked the cost of drugs (copays) directly to the risk of medical bankruptcy—it is the total cost of care that matters combined with other factors, such as loss of income.33 This is not to say that funding cancer treatment is easy; in fact, a diagnosis of myeloma poses a very substantial financial challenge to patients and their families, but an objective analysis of this hardship is rarely done. Furthermore, even in countries, such as Canada, that have both a national health system and bankruptcy protection laws (most countries do not have them), the risk of cancer and medical bankruptcy is high.34 The conjecture that the price of drugs and associated copays causes most medical bankruptcy fails the most basic scrutiny.

Copays exist to create a more discriminant purchaser (in this case, the patient) and indirectly aim to incentivize use of drugs with lower cost-sharing as well as reduce insurers’ liability for expenditures (dual aims that health economists have long criticized as not only flawed but also, incentives at cross purposes).35 Many problems exist with the current framework of copays. How a copay’s consumeristic pressure can be of help when there are no equivalent options (e.g., for drugs with market exclusivity and no therapeutic equivalents) is unclear.36 Drug copays have been proven, in economic analysis, to be a bad idea that fails to create value.35 To overcome this hurdle, manufacturers of drugs have created copay assistance programs for those with commercial insurance.37 As a result, a substantial majority of individuals only pay a nominal monthly fee as a copay. For instance, the current programs dispense a monthly supply of lenalidomide for as maximum copay of $25 to all commercially
insured patients who qualify, excepting those in a high-income bracket. Critics of this system fail to recognize that copay assistance programs function akin to a rebate given directly to patients. The same rebates have been implemented for other patented drugs used for the treatment of myeloma. A study by one specialty pharmacy, Diplomat, showed in a study of close to 80,000 prescriptions filled that the average copay for patients was $80 after financial assistance, and 86.2% of patients had a direct cost of less than $50. A total of 91% of patients pay less than $100 per month to access lenalidomide. For some families, this amount may still create a hardship but hardly what most news headlines claim.

The greatest problem with patient liability for cost-sharing is among the Medicare population, particularly those facing substantial out-of-pocket spending for Part D medications or those without supplemental insurance for Part B coverage, which leaves the beneficiary responsible for 20% coinsurance. Stark laws prevent direct copay assistance from pharmaceutical companies for Medicare, Medicaid, other federally insured beneficiaries, and some individuals insured by state government programs, and thus, financial assistance to these populations is only available when it can be obtained via a third party (usually a patient foundation or an organization, such as the Leukemia and Lymphoma Society). These nonprofit organizations administer funds granted by donors, which often include pharmaceutical companies and their foundations, to provide assistance for patient copays. Absent this system, many elderly and lower-income patients would not be able to afford prescribed drugs. Among industry critics, there is a visceral negative reaction to this method of patient financial assistance, and federal authorities have engaged in the investigation of these schemes as somewhat nefarious, particularly when a manufacturer’s funding supports patients in narrowly specific disease areas. It is remarkable that medical bioethicists have failed to call out the unnecessary financial distress introduced on a vulnerable population of patients with cancer facing life-limiting illnesses, often with limited economic means, who access foundation support for these purposes. In fact, these patients only have to access this financial support because of insurance benefit designs that fail to fully insulate them from financial hardship, which is the true purpose of health insurance.

Although the use of specialty drugs has greatly increased, they still are only a small fraction of all prescriptions, although most of the net cost increase in medications is associated with this group of medicines. A recent study by Dusetzina reports that, in 2014, the average copay for patients for specialty medications was $35. There is a disconnect between the rhetoric about hardship to patients and reality. As should be obvious now, the vast majority of manuscripts addressing hardship associated with copays focus on Medicare beneficiaries, often those without supplemental insurance to Part B coverage, which leaves the beneficiary with a 20% coinsurance on all claims, or those in the Part D “donut hole.” Using the same database used by Dusetzina, we found that the cost of care for myeloma increased over time from 2000 to 2014. In 2000, myeloma treatment–related drug costs accounted for 10.6% of total health care costs, increasing to 20.3% in 2007 and 28.5% in 2014 ($4,179 per patient per month). However, drug costs did not outpace the cost for hospitalizations and other outpatient interventions.

“DANGER ZONES”—PITFALLS OF PROPOSED SOLUTIONS

Formularies, Pathways, and Other Usage Restrictions

One proposed way to control prices is the introduction of boundaries in the form of pathways, formularies, or other administrative strategies that would aim to curtail the use of expensive medications. These can be in the form of guidelines (such as those of the National Comprehensive Cancer Network) or mandates (such as pathways in closed systems). The more restrictive versions include formularies that either deny coverage or make it only accessible at a steep price for patients. Some insurer programs reward physicians for prescribing from a narrowed formulary, often without transparency to the patient being treated that the prescriber may be gaining a bonus for restricting treatment options. For instance, a review of drugs available in the formulary of the Veterans Administration system shows that some of the newest and by corollary, most expensive drugs were not available to beneficiaries, whereas they were covered under formularies of other payers. Outside of the United States and undoubtedly, as a cost-containment strategy, many cancer drugs are either approved at a much later date or approved but not provided coverage for funding. This delay is observed even in advanced economies with a per capita gross domestic product similar to that of the United States, such as those in the European Union. Based on conclusive clinical trial data, lenalidomide was approved in the United States for the treatment of relapsed and refractory myeloma in December of 2005. Many years later, the drug was either not approved or not funded in many European countries. In countries with strong emergent economies, it has taken more than a decade for these drugs to become available. Lenalidomide was just recently approved in Brazil. In the past, any patient wishing to receive lenalidomide had to sue the government to gain access.

Price Controls and Medicare Negotiation

Price and wage controls have been shown, extensively and empirically, not to be a good solution to set ideal prices. One strategy that has been proposed to decrease the cost of drugs has been to “allow Medicare to negotiate prices.” This strategy is more of an abstract aspiration of artificial setting of prices rather than negotiation. For Part D, Medicare delegates the negotiation functions to plans that administer drug benefits to its beneficiaries. Similar direct negotiations have been conducted in the past and have failed. Given that private insurance companies already negotiate prices on behalf of their beneficiaries, it is unclear how Medicare can further improve on these negotiations, salvo two exceptions: create exclusionary formularies (like the National Institute for Health and Care Excellence in the
United Kingdom) with a willingness to decisively not cover therapies that do not meet certain cost criteria or set prices artificially (price controls).\textsuperscript{47} No matter how sophisticated a proposed hypothesis is for a correct price, history has repeatedly shown that artificial interference with the market will only lead to scarcity.\textsuperscript{48} Market distortions have recently lead to shortages in cancer essential medications, all of them generic and mostly injectable. We have yet to witness a shortage of lenalidomide, bortezomib, carfilzomib, daratumumab, ixazomib, denosumab, or one of the many drugs available for the treatment of myeloma. Meddle with prices, and this may very well happen.

**Eminent Domain and Compulsory Licensing**

Some have proposed to exercise eminent domain rights and set the prices of medications to better perceived value.\textsuperscript{49} Others have stated that, at the international level, compulsory licensing is necessary to overcome the economic burden of the high cost of these drugs for poor countries. Although debatable, a clear argument can be presented against the obvious moral implications of coercively obtaining something (intellectual property). Ethically, this could be countered with an argument that it is morally wrong not to extend the benefit of current therapies to those in need, and thus, there is the need for these actions, particularly in situations of public health crisis. Drug development happens in the Western world, predominantly in the United States, and exists in a system that rewards innovation and investment with a period of exclusivity granted by the patent system. This patent system does not imply monopolistic forces, because parallel drug development is always possible (e.g., isatuximab and daratumumab). If the current drug development system was to be challenged by eminent domain or compulsory licensing, there would likely be a deeply negative effect on further investment in innovation, particularly if risk exists for parallel reimportation of drugs manufactured in low-income countries under a compulsory license.\textsuperscript{40} The economic literature shows conclusively that limitations of possible economic reward will stymie innovation and investment.\textsuperscript{50-52} Ironically, we are fortunate in that successful investments in cancer drug development have attracted further investment from others. Although undoubtedly, this “bullish” environment is of benefit to the investors, it is also ultimately beneficial to those affected with cancer who reap the rewards of more treatment options and shorter intervals between new discoveries. Unfortunately, this is not currently the case in Alzheimer disease and other neurodegenerative diseases, where there is worry about return on further investment in clinical trials because of a number of recent setbacks in clinical development. Moreover, if we were to interfere with the current system, investment may migrate to other more lucrative aspects of the economy and stymie growth in biomedical innovation.

**INTERNATIONAL CONSIDERATIONS**

Patients in the United States pay a higher price for drugs than people in the rest of the world: both generics and those protected by patents. Arguably, a global approach that allows access to cheap generics is desirable and only must be substantiated by the necessary quality control metrics to establish confidence in the products. Such a system should not be hard to accomplish (by allowing free market forces to operate) and could reduce prices for medications on the U.S. market as long as manufacturing practices are able to meet FDA standards. Furthermore, a rapid transition from a patented status to generic is essential in a holistic model, where respect for intellectual property protects patented products, and yet, widespread access to cheaper generics is a future reality. There are some legitimate concerns about the quality of generics manufactured abroad given that some studies suggest a lack of an active agent in up to 10% of agents or wide variations of potency or purity; however, these barriers can be overcome with oversight.

In contrast, importation of patented medications is intellectually dishonest and inconsistent with the current model of protection of intellectual properties. Moreover, parallel import is a potential channel for the introduction of counterfeit or fraudulent drug product into the U.S. supply chain. Although some have insinuated that other countries are better negotiators than American purchasers, the reality is that the current system of drug development makes the U.S. population subsidize drugs for the rest of the world.\textsuperscript{53} The majority of profit generated with patented medications is realized in the United States. In return, U.S. patients have earlier access to medications in most instances. Willingness outside of the United States to pay for drugs at similar prices to those in the United States would no doubt result in simultaneous access elsewhere. It is possible, not assured, that similar pricing in high-income countries could result in lowering of prices, with resulting benefits to payers. If this scheme was not successful and prices became elevated abroad, this would further accelerate investment in drug development given the greater reward, even if the fractional sales abroad dropped. Future economic analysis could easily conclude that the transfer of wealth and opportunities created by the artificially low prices paid by advanced economies for newer medications saved lives and represented a great act of benevolence by the United States.

Selecting unique situations or corporations that have exceeded the financial success of the market is unfair in that it omits mention of the failure of the many other commercial endeavors in drug development; sadly, most compounds fail.

**CONCLUSION**

Oncologists and cancer researchers find the strength to persist in their quest because of the optimism for a better future. The cost of care for myeloma is high and growing. The economic challenges faced by someone with myeloma are daunting, but their prospects for a better future continue to improve. Despite the growing cost of drugs, patients with myeloma can have access to these medications in the United States. These authors have not encountered a situation
where we could not dispense one of the myeloma drugs to our patients. Moreover, in providing medications to patients, we can improve their outlook. The advent of immunotherapies, such as CAR T cells, will only increase the cost of care, but it will also increase the possibility of patients being long-term survivors, and perhaps, a sizable number could be cured. Those of us caring for patients with myeloma know that we are a “new drug away” or a “combination away” from having a regimen equivalent to what R-CHOP is for lymphoma. Long-term studies have shown that, even with transplant, a small minority of patients can be cured. Perhaps an optimal induction (e.g., daratumumab1 plus carfilzomib, lenalidomide and dexamethasone) followed (or not) by consolidation (with stem cells transplant or CART) will cure more patients. If so, the future will not only be brighter, but it will also be more economical. We cannot afford to lose momentum, and we can afford these drugs.

References


The treatment of MM has changed dramatically in the past decade with the introduction of new drugs into therapeutic strategies both in the frontline and relapse settings. With the availability of at least six different classes of agents that can be combined in doublet, triplet, or even quadruplet regimens and used together with high-dose therapy and autologous stem cell transplantation, the choice of the optimal strategy at diagnosis and at relapse represents a challenge for physicians. Also problematic is the lack of trials addressing questions, such as sequencing or the duration of maintenance. This review will focus on the results of recent clinical trials both in the frontline and relapse settings that have induced changes in clinical practice and will discuss the impact of important ongoing trials. A specific section will discuss therapeutic strategies when new drugs are not available.

Cost and drug access are crucial issues. Drugs recently approved by regulatory agencies in Europe, the United States, or Japan are not available in South America, Africa, or parts of the Asia Pacific region and European Union. Therefore, guidelines developed by the European Society for Medical Oncology and the National Comprehensive Cancer Network are not universally applicable, and alternative, cost-effective strategies should be proposed.

This review will focus on the results of recent clinical trials both in the frontline and relapse settings that have induced changes in clinical practice and discuss the impact of important ongoing trials. A specific section will discuss therapeutic strategies when new drugs are not available.

FRONTLINE THERAPY IN PATIENTS NOT ELIGIBLE FOR ASCT

Recent Important Phase III Clinical Trials

Three important studies have been reported in the past 2 years to establish new standards of care.

The FIRST trial prospectively examined outcomes in patients treated with lenalidomide and low-dose dexamethasone until disease progression (Rd continuous; 535 patients), Rd for 72 weeks (18 cycles [Rd18]; 541 patients), or melphalan, prednisone, and thalidomide (MPT; 72 weeks; 547 patients). At a median follow-up of 67 months, progression-free survival (PFS) was significantly longer with Rd continuous versus MPT (hazard ratio [HR], 0.69; p < .00001). Rd continuous also reduced the risk of progression or death compared with Rd18 (HR 0.70). The median PFS was 26.0
months with Rd continuous, 21.0 months with Rd18, and 21.9 months with MPT. Median OS was 10 months longer with Rd continuous versus MPT (59.1 vs. 49.1 months; HR 0.78; \( p = .0144 \)) and similar with Rd18 (62.3 months). This study clearly demonstrates the superiority of Rd over MPT and supports Rd as a standard of care for patients with transplant-ineligible newly diagnosed MM. The lack of OS difference in the two Rd arms also suggests that Rd may be stopped after 18 cycles in case of toxicity or poor tolerance.

Rd has also been prospectively compared with the triplet combination Rd plus bortezomib (VRd) in symptomatic patients with previously untreated MM who were not planned with Rd continuous versus MPT (59.1 vs. 49.1 months; HR 21.9 months with MPT. Median OS was 10 months longer is a potent frontline option and might be proposed in fit elderly patients with the combination of a PI and an immunomodulatory agent

64 months: HR 0.709, \( p = .025 \). These results suggest that the addition of daratumumab to VMP results in a lower risk of disease progression or death compared with VMP. This quadruplet combination is not yet approved, but, once available, might become another standard of care for patients with newly diagnosed MM not eligible for ASCT.

Overall, based on the results of recent phase III trials, four regimens (i.e., Rd, VRd, VMP, and VMP plus daratumumab) may be considered as backbone regimens in the frontline therapy of elderly patients.

**Ongoing Trials That May Change the Therapeutic Landscape**

Three trials have been completed, and their results, awaited in the next months, might change future guidelines. In these trials, Rd continuous was compared with Rd plus daratumumab, elotuzumab, or ixazomib. These trials might establish triplet Rd-based combinations as standards of care.

**Open Issues and Challenges in the Management of Disease in Nontransplant-Eligible Newly Diagnosed Patients With Multiple Myeloma**

In patients older than age 65 to 70, the majority of newly diagnosed symptomatic cases, newer regimens have increased overall response, PFS, and OS rates. Nevertheless, there is no plateau in the survival curves, and the probability of cure is low. In this setting, the issue of the duration of frontline therapy, fixed versus continuous until progression, is crucial. As discussed previously, in the FIRST trial, there was no OS difference between the two Rd arms (Rd continuous and Rd18). The concept of drug holidays with a fixed duration of therapy in responding patients, aiming to avoid toxicity, improving quality of life, and saving costs, should be evaluated in future trials.

Moreover, elderly patients represent a highly heterogeneous group that is not able to tolerate one universal strategy. Several geriatric scores, evaluating factors—such as comorbidities, performance status, mental status, activities of daily living, instrumental activities of daily living, polypharmacy, and renal and lung functions, etc.—have been proposed. To recommend an adequate strategy to a specific patient, we need a simple and time-efficient tool to evaluate patient status, including comorbidities and physical, cognitive, and social conditions. We also need trials focusing on subgroups of patients with different frailty scores.

The management of disease in patients with high-risk cytogenetics remains an important challenge. Until now, no specific large trials have been conducted in this population. In the FIRST study, the subgroup of patients with high-risk cytogenetics did not experience an OS benefit with Rd continuous versus MPT. In the ALCYONE trial, the PFS of patients with high-risk cytogenetics at diagnosis was improved with the addition of daratumumab to VMP; however, the number of patients was small. Cytogenetic data were not available in the trial comparing Rd versus VRd, but data from the large phase II study conducted by the Spanish group, which evaluated Rd plus VMP as frontline therapy, suggest that the prolonged combination of a PI and an

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**PRACTICAL APPLICATIONS**

- Based on the results of recent phase III trials, four regimens (i.e., Rd, VRd, VMP, and VMP plus daratumumab) may be considered as backbone regimens in the frontline therapy of elderly patients.
- For patients in good clinical condition, induction followed by high-dose therapy with ASCT followed by maintenance is the standard treatment according to the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.
- For patients with relapsed myeloma, two carfilzomib-containing regimens (i.e., KRd and carfilzomib in combination with dexamethasone) showed recently overall survival benefit over current standard therapies. Additionally, two trials tested daratumumab in combination with either Vd or Rd in a randomized fashion and showed unprecedented hazard ratios for progression-free survival.
- For patients with high-risk smoldering myeloma, clinical trials aimed at preventing the progression to MM are underway, with some trials even aiming for cure.
immunomodulatory agent might overcome the poor prognosis of high-risk cytogenetics in elderly patients.\textsuperscript{12}

Finally, preliminary results from ALCYONE indicate that the achievement of MRD negativity matters in elderly patients.\textsuperscript{10} A negative MRD status was associated with a longer PFS than MRD-positive status, irrespective of the treatment arm. With the availability of more potent combinations, studies focusing on the achievement of MRD negativity should be designed in the future.

**FRONTLINE THERAPY IN PATIENTS ELIGIBLE FOR ASCT**

**Guidelines**

For patients in good clinical condition, induction followed by high-dose therapy with ASCT followed by maintenance is the standard treatment according to the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines.\textsuperscript{1,2} Triplet combinations including at least bortezomib and dexamethasone present the backbone of induction. Lenalidomide, bortezomib, and dexamethasone are the standard of care in the United States and some non-U.S. countries. Bortezomib, thalidomide, and dexamethasone are widely used in Europe, and bortezomib, cyclophosphamide, and dexamethasone (VCD), which are generally available, may also be used prior to ASCT. Four to six courses of induction are recommended before proceeding to stem cell collection, with melphalan 200 mg/m\textsuperscript{2} as a conditioning regimen. After ASCT, lenalidomide maintenance treatment is recommended.\textsuperscript{1,2}

**Open Issues and Challenges in the Management of Disease in Transplant-Eligible Newly Diagnosed Patients With Multiple Myeloma**

One of the most challenging questions is: can we reserve ASCT until the time of the first relapse? Two recent phase III trials comparing frontline ASCT versus ASCT at the time of first relapse showed that PFS was improved in the frontline ASCT arm. In the IFM2009 trial, the median PFS was 50 months in the RVd plus ASCT arm versus 36 months in the arm receiving lenalidomide, bortezomib, and dexamethasone alone (HR 0.65; \( p < .001 \)).\textsuperscript{13} Transplantation was associated with increased MRD negativity, but OS was similar in the two arms (4-year survival of 81% in the transplant group vs. 82% in the lenalidomide, bortezomib, and dexamethasone group). In the EMN02 trial, PFS was superior in the VCD plus ASCT arm (median not reached, 64% at 3 years) versus a median of 44 months in the VCD/VMP arm (HR 0.76; \( p < .002 \)). Without an OS difference (86% at 3 years in both arms),\textsuperscript{14} Despite a difference in PFS, the absence of an OS benefit in both trials allows for a consideration of patient preference regarding the timing of the ASCT procedure. The clear correlation between MRD negativity and OS in the IFM2009 trial\textsuperscript{13} strongly supports the routine implementation of MRD assessment in future trials to guide treatment decisions.

The second issue is the role of consolidation after ASCT. Consolidation may include short-term novel agent-based combinations, a second ASCT procedure, or the combination of tandem ASCT plus a novel agent-based combination. The prospective StaMINA study conducted in the United States evaluated no consolidation (257 patients) versus four cycles of VRD (254 patients) versus a second ASCT (247 patients) after frontline ASCT.\textsuperscript{15} All patients subsequently received lenalidomide maintenance. At 38 months follow-up, there was no difference in PFS or OS among the three arms. The preliminary results of the StaMINA trial suggest that consolidation consisting either of novel agents or tandem ASCT has no benefit. In contrast, in the prospective EMN02 trial conducted in Europe, tandem ASCT (207 patients) was associated with a superior PFS compared with single ASCT (208 patients; 72.5% vs. 64% at 3 years [HR 0.71; \( p = .04 \)]) at a median follow-up of 3 years.\textsuperscript{16} This PFS benefit translated into an OS benefit: 88.9% at 3 years in the tandem ASCT arm versus 81.5% for single ASCT (HR 0.51; \( p = .01 \)). The survival benefit was also considerable in patients with high-risk cytogenetics (HR 0.48). The same study incorporated a second randomization step after induction with or without ASCT, which consisted of VRD given for two cycles (450 patients) versus no VRD consolidation (435 patients).\textsuperscript{17} With a median follow-up of 25 months, the PFS was significantly improved in the VRD arm (HR 0.78), without a difference in OS. Overall, the EMN02 data suggest that tandem ASCT may be important, especially for patients with high-risk cytogenetics.\textsuperscript{16} The divergent results of the U.S. and European trials indicate that longer follow-up is needed before final conclusions can be drawn.

How to improve now on the results of frontline ASCT? In the induction phase, studies are underway investigating the use of carfilzomib instead of bortezomib in combination with Rd or the addition of daratumumab to the standard bortezomib, thalidomide, and dexamethasone regimen, as in the prospective CASSIOPEIA study. Another study comparing VRD with or without daratumumab followed by ASCT will start soon. To examine whether the conditioning phase can be improved, the Spanish group is currently conducting a prospective study comparing melphalan 200 mg/m\textsuperscript{2} versus melphalan plus busulfan (GEM12). The maintenance phase is also under active investigation. The Italian group is conducting a study to prospectively compare lenalidomide to lenalidomide plus carfilzomib, whereas the Spanish group is investigating the combination of lenalidomide plus ixazomib compared with lenalidomide alone. The optimal duration of maintenance is a frequent question raised by patients and physicians. A comparison of the results of the IFM2009 trial\textsuperscript{13} (lenalidomide maintenance for 1 year) and those of the Dana-Farber Cancer Institute trial (lenalidomide maintenance until progression)\textsuperscript{18} will help in solving this issue.

The implementation of an optimal strategy, consisting of novel agent-based induction, high-dose therapy followed by ASCT, and the use of novel agents in consolidation and/or maintenance, already result in a 5-year survival rate of 80%, and cure might be considered in a subset of patients, who present with standard-risk features at the time of diagnosis. The achievement of cure will require sustained MRD
negativity, assessed at several time points during therapy. In an ongoing study, the Spanish group is evaluating MRD by NGF after induction, after ASCT, after consolidation, and at several time points during maintenance to validate this concept. Of note, data from the IFM2009 trial show that MRD should be assessed not only within the bone marrow using either next-generation sequencing or NGF, but also using an imaging technique, such as PET-CT. Patients with MRD-negative disease both by flow and PET-CT had a significantly better PFS as compared with those patients with either PET-CT and/or flow positivity.

**RELAPSED MULTIPLE MYELOMA**

**Recent Important Phase III Trials**

Until recently, bortezomib plus dexamethasone (Vd) or Rd were the typical regimens at first or second relapse. In the last 3 to 4 years, several phase III randomized trials have shown improvements in PFS and/or OS with the use of carfilzomib (K), ixazomib (I), daratumumab (D), elotuzumab, or panobinostat. We now have a long and varied list of options at our disposal, including Vd, Vd plus panobinostat, daratumumab with bortezomib plus dexamethasone (DVd), carfilzomib in combination with dexamethasone, Rd, Rd plus elotuzumab, carfilzomib with lenalidomide and dexamethasone (KRd), ixazomib with lenalidomide plus dexamethasone, and daratumumab with lenalidomide plus dexamethasone (DRd), all approved by the U.S. Food and Drug Administration and the European Medicines Agency.

Among those options, two have shown an OS benefit versus control therapy in phase III trials, and two have achieved unprecedented HRs. The ENDEAVOR trial, which prospectively compared carfilzomib in combination with dexamethasone (464 patients) versus Vd (465 patients) in patients with one to three prior lines of therapy, showed that patients treated with carfilzomib (56 mg/m²) and dexamethasone had a statistically significant improvement in OS over patients treated with Vd (median 47.6 vs. 40.0 months; HR 0.79; p = .01). The OS benefit was consistent, regardless of prior bortezomib therapy, number of prior regimens, age, and cytogenetic risk group. Moreover, the ASPIRE trial, which prospectively compared KRd (396 patients) versus Rd (396 patients) in patients with one to three prior lines of therapy, showed that patients treated with carfilzomib (27 mg/m²) plus Rd had a statistically significant improvement in OS compared with patients treated with Rd (median OS 48.3 months for KRd vs. 40.4 months for Rd; HR 0.79; p = .0045). The advantage in efficacy demonstrated by KRd is most pronounced at first relapse (among those patients, the median OS was 11.4 months longer for KRd vs. Rd, whereas it was 6.5 months longer for KRd vs. Rd among patients having received more than two prior lines of therapy). The OS benefit observed for a carfilzomib-containing regimen over current standard therapies represents an important finding. More recently, two trials tested daratumumab in combination with either Vd or Rd in a randomized fashion and showed unprecedented HRs for PFS. The CASTOR study prospectively compared Vd (247 patients) versus DVd (251 patients). The 12-month PFS rate was 60.7% in the daratumumab group versus 26.9% in the control group. After a median follow-up period of 7.4 months, the median PFS was not reached in the daratumumab group and was 7.2 months in the control group (HR 0.39; p < .001). OS data are not yet mature, but DVd is already approved by the Food and Drug Administration and European Medicines Agency, and this triplet combination will become a standard in the relapse setting, when available and reimbursed. Furthermore, the POLLUX study prospectively compared Rd (283 patients) versus DRd (286 patients). PFS at 12 months was 83.2% in the daratumumab group, as compared with 60.1% in the control group (HR 0.37; p < .001). In the daratumumab group, 22.4% of the patients had results below the threshold for the detection of MRD (1 tumor cell per 10⁶ white cells) versus 4.6% of those in the control group (p < .001). Of note, results below the threshold for the detection of MRD were associated with improved outcomes. DRd is also approved by the Food and Drug Administration and European Medicines Agency and will soon play a key role in relapsed MM.

**Open Issues and Challenges in the Management of Relapsed Multiple Myeloma**

Drug access and reimbursement of carfilzomib in combination with dexamethasone, DVd, DRd, or KRd, the most active regimens in the relapse setting, will be important issues. The same is true for ixazomib with lenalidomide plus dexamethasone or elotuzumab plus Rd. One way to reduce cost could be the use of a fixed duration of therapy, instead of the application of treatment until progression. All recent phase III trials have followed the same design: PFS as a primary endpoint and treatment until progression. We should recommend trials asking strategic questions, such as: can combination regimens be developed that are given for a fixed duration and that are as effective as continuous therapy? Or, what is the most cost-effective triplet regimen to be used at relapse?

Treatment at relapse is selected according to the first-line treatment and the duration of the first response, among other criteria. Following the recent approval of Rd until progression (in elderly patients) and lenalidomide maintenance after ASCT until progression, many patients will progress while receiving lenalidomide. In this situation, the switch to a PI-based combination as salvage therapy will be a logical approach. We must develop trials integrating the first salvage regimen into the assessment of frontline therapies to define the optimal sequencing strategies and evaluating time to second-objective disease progression as an important endpoint.

The impressive HRs of POLLUX and CASTOR present a challenge for the development of new agents in relapsed MM. Despite the promising activity of venetoclax or se-linexor, for example, one cannot anticipate that an experimental arm including these two agents will be superior to DRd or DVd in a phase III trial. New agents are typically initially examined in patients with end-stage, refractory
disease. Their evaluation earlier in the disease course in patients who progress after one line of therapy will require innovative study designs or the restriction to specific genetic subtypes or to a patient population selected via a specific biomarker predicting efficacy and response to therapy.

**High-Risk Smoldering Myeloma**

For patients with smoldering MM, the current standard of care is “watch and wait.” Nevertheless, the entity is heterogeneous, with a subgroup of patients who have a short time of progression to MM. For these patients with high-risk smoldering MM, clinical trials aimed at preventing the progression to MM are underway, with some trials even aiming for cure.

**Ongoing or Future Important Clinical Trials**

One of the trials aimed at delaying the progression of high-risk smoldering MM to symptomatic MM was reported in the 2017 meeting of the American Society of Hematology. In the phase II CENTAURUS study, three different dosing schedules of daratumumab were evaluated in 123 patients (41 in each arm): a long regimen (weekly daratumumab in cycle 1, every other week in cycles 2 and 3, every 4 weeks in cycles 4 through 7, and every 8 weeks up to cycle 20); an intermediate schedule (weekly daratumumab in cycle 1 and every 8 weeks up to cycle 20); and a short, intense dosing schedule (weekly daratumumab for 1 cycle). The 12-month PFS rates were 95% with the long schedule, 88% with the intermediate-dosing schedule, and 81% with the short intense schedule. More than half (54%) of the patients in the long arm and 49% in the intermediate arm had a partial response or better. In the short arm, 38% of patients had a partial response or better. The complete response rate was less than 15% in each arm, missing the complete response coprimary endpoint. The progression/death rate surpassed the goal of 24 months or more in all three arms. It is unlikely that daratumumab single-agent will cure high-risk smoldering MM, but it may delay the progression of the disease. The long dosing schedule is being investigated in the ongoing phase III AQUILA study. Also at the 2017 meeting of the American Society of Hematology, the Spanish group reported the preliminary results of the CESAR trial, which is aimed at curing selected patients with high-risk smoldering MM. In this phase II single-arm trial, 90 patients younger than age 70 and eligible for transplantation were included. Induction therapy consisted of six 4-week cycles of KRd. Patients received melphalan (200 mg/m²) conditioning and ASCT. Thalidomide maintenance may be proposed after ASCT.

**THERAPEUTIC STRATEGIES WHEN NEW DRUGS ARE NOT AVAILABLE**

**Frontline Therapy**

In many countries, lenalidomide is not available as part of frontline treatment. In elderly patients not eligible for ASCT, VMP is the preferred option. Bortezomib may also be combined with cyclophosphamide and dexamethasone (known as VCD) or prednisone. When bortezomib is not available, an alkylation may be combined with thalidomide in the MPT or cyclophosphamide and dexamethasone regimen. Six to nine cycles of induction therapy are recommended. When high-dose therapy is available, younger fit patients up to age 70 may receive four to six cycles of VCD or bortezomib, thalidomide, and dexamethasone followed by melphalan (200 mg/m²) conditioning and ASCT. Thalidomide maintenance may be proposed after ASCT.

**Therapy in the Relapse Setting**

Different scenarios may be discussed according to lenalidomide and bortezomib availability. When bortezomib is available as an option for frontline treatment, and lenalidomide is available only at relapse, Rd (or Rd plus cyclophosphamide) presents the best choice at relapse. Otherwise, retreatment with the frontline regimen is an option, if the duration of the first response was at least 1 year. If ASCT is available and was not used as part of frontline therapy, patients may receive ASCT at relapse. ASCT may also be proposed as salvage therapy after frontline high-dose treatment, if PFS was longer than 2 years.

In case lenalidomide is not available at all, whereas bortezomib is available at relapse only, Vd or VCD are the recommended options at relapse. Retreatment with the frontline regimen is an option if the duration of the first response was at least 1 year.

**Open Issues and Challenges in Countries With Limited Access to New Agents**

Drug access is mostly related to drug coverage and cost. A triplet combination, such as VRD, can cost more than $150,000 per person per year (in U.S. dollars). Triplets that incorporate drugs such as carfilzomib or daratumumab even exceed these costs. Future regimens are likely to be even more expensive. Given these high costs, how many patients worldwide have access to such regimens? This is especially challenging when drugs or combinations are intended to be administered until progression. All of those involved in the process of drug development and drug access should make a concerted effort to tackle the high cost of cancer drugs and deliver the most cost-effective therapy. The research community should exert their influence to pressure pharmaceutical companies into reducing cost and needs to support the development of effective generic drugs.
References


The treatment of multiple myeloma has improved significantly over the past 10 to 15 years, more than doubling the overall survival of the disease.\(^1,2\) In the recent IFM trial, the 4-year survival rate of patients with myeloma was 82% using standard therapy with bortezomib, lenalidomide, and dexamethasone, autologous stem cell transplantation, and lenalidomide maintenance.\(^3\) In fact, even these results underestimate what is possible today, as they do not take into account the arrival of the monoclonal antibodies daratumumab and elotuzumab.\(^4\) However, modern treatments are useful only if patients in the real world have access to them. The standard initial therapy available to well-insured patients in the United States (bortezomib, lenalidomide, and dexamethasone) is not available to most newly diagnosed patients in most countries.\(^5\) Regulatory barriers aside, an important factor that prevents access is the prohibitive cost of most myeloma drugs.\(^5\) Even when access is not a problem, and when out-of-pocket costs are almost completely covered by private insurance or the public health system, the high costs are not sustainable for any country.\(^5-8\) Table 1 lists the annual cost of myeloma therapy for each active drug. Because myeloma therapy is mostly administered as a combination of three or more drugs, the costs of common combinations are also provided. The information presented needs no explanation or justification: it speaks for itself. Patients with myeloma are treated for years in a continuous manner. With median survival in excess of 7 to 10 years, one can do the math in terms of cost. Myeloma is a great example of a problem that plagues all cancers.\(^5\) Almost every approved new cancer drug costs more than $100,000 per year in the United States.\(^9,10\) Although this article is focused on the cost of myeloma drugs, clearly there are other issues that must be addressed, including the cost of laboratory workup and imaging, physician visits, chemotherapy administration, hospital charges, and so on.

**WHY ARE CANCER DRUGS SO EXPENSIVE?**

The high cost of cancer drugs is related to multiple factors, and they are to some extent similar in most countries.\(^11-13\) However, there are special problems that are unique to the United States: prolonged monopoly protection, inability of Medicare to negotiate price of drugs directly with pharmaceutical companies, a ban on the importation of drugs for personal or public use, among others. The major factors that contribute to the high cost of cancer drugs in the United States are listed in Sidebar 1.

**Cost of Drug Development**

Drug development is costly and carries substantial risk. Many drugs must be investigated in preclinical and clinical studies to find one winner. The cost of translating findings from bench to bedside, performing regulatory studies needed to gain approval, conducting subsequent confirmatory studies, and postapproval safety monitoring are all high.\(^14\) Pharmaceutical companies therefore try to regain investment by adding costs of development of both successful and unsuccessful products to the newly approved drug. Prasad and Mailankody\(^15\) estimated that the cost to develop a cancer drug is $648 million. This is much lower than other estimates but is nevertheless illustrative of the high cost that needs to be recovered when a new successful drug is marketed.

**Virtual Monopoly**

When a new drug is approved, there is a lengthy period of patent protection that grants a company monopoly over the drug. In cancer, the drug in question is lifesaving, not a

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**OVERVIEW**

Major advances have occurred in the treatment of multiple myeloma, including several new drugs that typically cost more than $100,000 per year. Although the gains in myeloma therapy improve overall survival considerably, they are available to only a fraction of the population of patients with myeloma in the world because of regulatory barriers and cost. Myeloma is an example of what is happening in cancer on a much larger scale. Many of the problems discussed call for a wider discussion across all cancers, but they are amplified in myeloma because of the need for multidrug regimens that combine three or more expensive new drugs for prolonged periods of time. In this article, the reasons for the high cost of cancer drugs and possible solutions are examined. The lack of correlation of value and price, the remarkable rise in prices of existing old medications over time, and the lack of access to lifesaving drugs across various countries are also discussed.
VALUE AND COST OF MYELOMA THERAPY

luxury option that one can live without. Even when a new drug is one of many options for a given cancer, it does not limit the monopoly. Myeloma and most other cancers are not curable, and patients receive each approved new drug in sequence or in combination. Thus, although there are several active myeloma drugs, almost all patients with myeloma must try the new ones, making each new drug a virtual monopoly. As time passes, and the patent life nears an end, companies usually resort to a variety of proven strategies that extend the virtual monopoly. This includes “new and improved” versions to take the place of older, more toxic or inconvenient drugs, deals with generic pharmaceutical companies to delay the arrival of generics, legal challenges to generic entry, and so on. With poorly designed trials, it is possible to create the sense that the older drug is inferior.

Seriousness of Cancer

Cancer carries serious consequences. Families are vulnerable and are willing to do anything to make it go away, even when drugs are very expensive and provide only marginal improvements in outcomes. They often do not want to give up until all options are exhausted.

Third-Party Payers

In most developed countries, including the United States, patients are not the primary payers for drugs. This makes high prices easier to sustain in the pharmaceutical sector compared with other economic sectors in which the “client” must make a choice to buy or not on the basis of affordability.

Financial Incentives

In the United States, the system of reimbursement provides an incentive to administer more expensive chemotherapy and to keep prices high. Current Medicare reimbursement policies for Part B drugs provide higher reimbursement when more expensive drugs are administered. Attempts to change these policies have been met with resistance from pharmaceutical companies, as well as professional and patient support organizations. There are few allies in the fight to lower drug prices.

Legal Barriers

Legal barriers prevent the U.S. Food and Drug Administration from taking economic and cost-effectiveness considerations into account when approving new drugs. Laws prevent the Centers for Medicare & Medicaid Services from being able to negotiate the prices of new drugs. There is also a prohibition on the importation of drugs for personal use. Organizations such as the Patient-Centered Outcomes Research Institute, created by the Patient Protection and Affordable Care Act of 2010, are specifically prohibited from using cost-effectiveness measures in funding comparative effectiveness studies or in their recommendations. All of these ensure that there are no free-market economic checks to out-of-control prices.

HOW CAN WE REDUCE THE COST OF CANCER DRUGS?

The solution to the high cost of myeloma (and cancer) therapy requires bold initiatives and changes to existing law, particularly in the United States (Sidebar 1).
Value-Based Pricing
When we talk value-based pricing, we are not attempting to set a monetary value on a person’s life. Rather we are attempting to place a monetary value on a product to which we are granting monopoly protection. In a monopolistic situation without this step, the usual free-market principles based on quality, demand, and supply do not exist. Without some form of reasonable safeguard, there is nothing preventing prices from increasing year after year for no plausible reason, as they have for many years in multiple myeloma. In most European countries, Canada, and Australia, regulatory approval is only the first step. The price of the drug is then subject to negotiation on the basis of the value it provides. The value is estimated by assessing the clinical added value compared with existing drugs and a value estimate determined by calculating the number of quality-adjusted life-years gained with the new treatment and the incremental cost-effectiveness ratio. The World Health Organization has arbitrarily defined three times the gross domestic product per capita as a reasonable incremental cost-effectiveness ratio. At the prices proposed by pharmaceutical companies, the incremental cost-effectiveness ratios of all new myeloma treatments are far beyond this level. Absent value-based pricing, drugs that improve survival by only a few days or weeks can be priced at the same level as ones that provide a much larger degree of benefit.

The current system in the United States that allows a new drug to be marketed at a very high cost regardless of the value it provides is a disincentive for innovation. It is safer to develop a “me-too” drug than to engage in the risk taking needed to develop a truly innovative product.

Improved National Guidelines
Current cancer guidelines present a list of all possible or acceptable treatment options and serve primarily to ensure access or insurance coverage. Many guidelines include authors who have substantial financial conflicts of interest. These guidelines seldom provide recommendations on how to provide the most cost-effective care. Even when guidelines

SIDEBAR 1. Reasons for High Cost of Cancer Drugs and Possible Solutions

Why are cancer drugs so expensive?
• High cost of drug development
• Existence of virtual monopoly; lack of free-market competition
• Sustaining monopoly with “new and improved” versions of a drug as patents expire
• Willingness of patients to pay high costs even for marginal improvements in outcome because of the seriousness of the diagnosis
• Higher reimbursement to providers when more expensive drugs are administered
• Legal barriers that prevent the FDA from taking economic and cost-effectiveness considerations into account when approving new drugs
• Laws that prevent CMS from being able to negotiate the price of new drugs
• Prohibition of importation of drugs for personal use
• Resistance to change in policies from pharmaceutical companies and from professional and patient support organizations that receive financial support from pharmaceutical companies

What can we do about it?
• Value-based reimbursement and pricing
  ◦ FDA, CMS, or other agencies should be able to negotiate the sale price on the basis of the incremental value provided by the drug, as is done by health authorities in Canada and Europe
  ◦ PCORI should be authorized to allow cost-effectiveness as a metric to compare relative value of treatments
  ◦ Support organizations such as the Institute for Clinical and Economic Review that evaluate the cost-effectiveness and affordability of new treatments
• Negotiation of prices and formulary control
  ◦ CMS should be authorized to negotiate cost and have formulary control
  ◦ Strong advocacy and a patient-driven grassroots movement for the requires changes in federal law
• Increase market competition
  ◦ Allow importation of drugs for personal use
  ◦ Facilitate easier approval of generics
  ◦ Selectively invoke compulsory licensing provisions
• New modalities for drug development

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Abbreviations: CMS, Centers for Medicare & Medicaid Services; FDA, U.S. Food and Drug Administration; PCORI, Patient-Centered Outcomes Research Institute.
appear to be balanced, they can be easily used to advocate for the more expensive option, because rather than clearly stating a preference, they often present two drugs with vastly different prices as reasonable alternatives. We need evidence-based guidelines that critically examine the available data and not only provide clear recommendations that regimens are preferred but also identify regimens that should be avoided in a given setting if they lack adequate data on superiority compared with less expensive alternatives. The National Comprehensive Cancer Network (NCCN) has now initiated an effort to incorporate value-based recommendations into their guidelines, which represents a step in the right direction.

Medicare Negotiation of Drug Prices
Currently the Centers for Medicare & Medicaid Services are prevented by law from negotiating directly for the cost of cancer drugs administered through the Medicare Part D program. This, as expected, creates a situation ripe for annual price increases. As a result, pharmaceutical companies can set prices high and increase them periodically as well. We must authorize the Centers for Medicare & Medicaid Services to negotiate cost directly and make the system similar to those in Europe and Canada. However, this requires a change in existing law and will not be possible without strong advocacy and a patient-driven grassroots movement. We also must support recent efforts by the Centers for Medicare & Medicaid Services to test indication-based pricing and fixed reimbursement amounts for closely related drugs in a given class.

Increase Market Competition
Several measures can be adopted to increase market competition. First is to allow the importation of drugs from other countries for personal use. Second, we must make the approval of generics and biosimilars easier and prevent major pharmaceutical companies from engaging in a “pay-for-delay” strategy to delay the launch of a generic drug. Recent efforts by large health care organizations and other online retailers to enter the prescription drug industry will also foster more market competition. Finally, we must re-examine the length of patent protection and the attempts to further prolong patent protection by legal and other challenges.

Lower Drug Development Costs
Current drug approval requires randomized phase III trials. In the United States, a particularly promising drug can gain accelerated approval through phase II trials. In any case, the costs of these trials are exorbitant. Most of these costs are unnecessary and relate to an extraordinary amount of data collection, monitoring, and analysis. Given the risks involved, companies also play it safe by launching multiple trials, in the hope that one will succeed and lead to drug approval. If there is clear guidance on what is important, we can easily reduce these costs so that a new drug will not cost hundreds of millions of dollars to bring to market.

CONSEQUENCES OF THE HIGH COST OF MYELOMA DRUGS
Many of us working at major academic medical centers see a skewed population of patients who are well insured. For these patients, the personal costs are high, but not anywhere near how much an uninsured or international patient would pay for the same treatment. There is still a societal consequence. The high cost of myeloma therapy is passed on to the premiums of people without myeloma. Myeloma accounts for only 1% of all cancers, and it is not the only problem. All cancer drugs are expensive, and cancer is all too common. It is the dominant killer of our times. Thus, even if the selected patients we see pay only $50 or $100 copays for a $14,000 drug, the costs are being passed on to someone else through higher insurance premiums, higher taxes, and cutbacks to other important programs. Unless we have a scenario of infinite resources, this is not sustainable from a societal standpoint.
For uninsured or underinsured patients, the consequences are more personal. They may cut back on dose or schedule. They may lack access to the newest options. Sadly, they may not know that these options exist. Many countries whose patients participated in phase III trials that helped us obtain rapid approval of myeloma drugs do not have these drugs available for their own citizens. Some of this is related to regulatory barriers. But often these regulatory barriers are erected because of cost and budgetary constraints.
More problems loom on the horizon. Carfilzomib/lenalidomide/dexamethasone as initial therapy will cost approximately 1.5 to 2 times as much as bortezomib, lenalidomide, and dexamethasone. The likely addition of daratumumab, a highly active monoclonal antibody, to various triplet regimens currently in use for the treatment of myeloma will create quadruplets that could cost in excess of $300,000 to $500,000 per year (Table 1). Several other promising agents have shown single-agent activity in myeloma and will likely be approved for the treatment of the disease in the future. Once approved, these new drugs will greatly increase the number of rational combinations that are possible, as well as the inevitable associated costs.

CONCLUSIONS
It is thrilling to be part of the advances that have occurred in myeloma. We should celebrate them. Pharmaceutical companies working in collaboration with researchers have made these advances possible. But, currently, many of the advances are a reality to only a small proportion of well-insured, affluent patients with the disease. What need to change are the system and the legal framework so that myeloma drugs and other cancer drugs are more affordable and accessible.

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The monoclonal antibodies daratumumab and elotuzumab currently play a prominent role in the management of multiple myeloma (MM). Both have proven to be effective in combination regimens that incorporate other agents with established activity in this disease, and daratumumab monotherapy also has demonstrated great antitumor activity. With the rapid expansion of treatment options for MM in recent years, it is important to understand how best to use daratumumab and elotuzumab in the care of patients with MM. This article aims to provide perspective on this important aspect of MM management through a succinct review of the preclinical and clinical development of daratumumab and elotuzumab, general approaches to management of transplant-eligible and transplant-ineligible patients with MM, determinants of choice of therapy, challenges associated with use of monoclonal antibodies in myeloma, and future directions with monoclonal antibodies in MM.

TARGETS OF DARATUMUMAB AND ELOTUZUMAB: CD38 AND SLAMF7

CD38

CD38 is highly and uniformly expressed on MM cells; at relatively low levels on normal lymphoid and myeloid cells; and in some tissues of nonhematopoietic origin, such as prostatic epithelial cells, pancreatic islet cells, and airway-striated muscle. CD38 has ectoenzymactic activities and also receptor functions. Together, these qualities formed the rationale for the development of CD38 antibodies in MM. The first CD38 antibodies were developed in the early 1990s, but, although these agents had marked anti-MM activity, they were not evaluated in patients with MM. The first-in-class therapeutic antibody directed at CD38, daratumumab (fully human immunoglobulin [Ig] G1-kappa), was developed approximately 20 years later. Daratumumab was selected from a panel of 42 antibodies because of its marked activity against MM cells via complement-dependent cytotoxicity (CDC). Additional Fc-dependent immune effector mechanisms of daratumumab include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP). Furthermore, daratumumab induces programmed cell death via Fc-gamma receptor-mediated cross-linking. In addition, modulation of CD38 enzymatic activities may contribute to its anti-MM activity. These classic mechanisms of action are partly CD38 dependent, which explains why patients who achieve partial response or better with daratumumab monotherapy have higher CD38 expression on their tumor cells compared with patients who achieve less than partial response. However, CD38 expression on the cell surface is reduced rapidly after initiation of daratumumab treatment as a result of preferential killing of MM cells with high CD38 levels and also transfer of CD38-daratumumab complexes from tumor cells to immune effector cells in a process called trogocytosis. Because CD38 is uniformly reduced in patients with deep and durable remissions, CD38 reduction is not necessarily associated with escape from daratumumab treatment.

These observations also pointed to other modes of action of this antibody. Indeed, daratumumab also eliminates CD38+ regulatory T cells, regulatory B cells, and myeloid-derived suppressor cells. Importantly, the subset of CD38+...
regulatory T cells are more immunosuppressive in vitro than their CD38− counterparts.9 These changes in frequencies of immune suppressor cells result in CD4+ and CD8+ T-cell expansion with increased T-cell clonality and, potentially, a better host-antitumor immune response.9

On the basis of the high activity of daratumumab, several other anti-CD38 antibodies have been developed, including isatuximab (chimeric, IgG1-k). Besides killing MM cells by CDC, ADCC, and ADCP, this antibody also has strong pro-apoptotic activity independent of cross-linking agents.7,10 Furthermore, isatuximab induces MM cell death via the lysosomal-associated pathway.11 In vitro experiments showed that isatuximab also kills CD38− regulatory T cells, leading to improved immune effector function against MM cells,12 but it remains unknown whether isatuximab also has immunomodulatory activity in patients with MM. MOR202 (fully human IgG1-lambda) and TAK-079 (fully human IgG1) also target CD38. These antibodies kill CD38+ tumor cells via CDC, ADCC, and ADCP. Potential immunomodulatory activities of these agents are unknown.

**SLAMF7**

SLAMF7 is a glycoprotein that is highly expressed on the surface of MM cells irrespective of cytogenetic abnormalities or disease stage. It is also expressed on subsets of immune cells, including natural killer (NK) cells, where it functions as an activating receptor. Elotuzumab (humanized IgG1-k) is a first-in-class SLAMF7-targeting antibody. Elotuzumab exerts anti-MM activity by inducing NK cell–mediated ADCC.15,16 Furthermore, SLAMF7 ligation by elotuzumab results in direct NK cell activation.17

**ANTIBODY-BASED COMBINATIONS**

Patients with MM most often are treated with combinations of anti-MM agents to improve depth and duration of response and to prevent the outgrowth of drug resistant clones. Preclinical studies have produced valuable insights into synergistic antibody-based combinations and thereby formed the rationale for several clinical trials.

In vitro studies and mouse models demonstrated that proteasome inhibitors markedly enhance the effects of antibodies directed to CD38 or SLAMF7.16,18-22 Immunomodulatory drugs, such as lenalidomide and pomalidomide, have direct anti-MM activity but also have immunostimulatory effects that include NK cell activation and stimulation of T-cell proliferation.23 In vitro experiments demonstrated that IMiDs markedly improve the ADCC activity of both CD38- and SLAMF7-targeting antibodies via enhancing effector cell activity, whereas efficacy of antibodies to induce CDC remained unchanged.11,16,20,21,24,25 In addition, immunomodulatory drugs enhance the direct apoptotic activity of isatuximab.11 NK cell activity also can be enhanced by blocking their inhibitory killer cell immunoglobulin–like receptor (or KIR), which results in improved daratumumab-mediated ADCC.36 PD-1 is another inhibitory receptor expressed on both NK cells and T cells. Binding of PD-1 to PD-L1 or PD-L2 leads to an impaired antitumor immune response. It was shown recently that the efficacy of tumor-targeted antibodies, such as elotuzumab, can be improved by inhibition of the PD-1/PD-L1 pathway.27

Laboratory experiments showed synergy between daratumumab and low-dose cyclophosphamide, which was partly explained by low-dose cyclophosphamide–induced improvement of ADCP mediated by monocytes and macrophages.28 ADCP also can be enhanced by inhibition of the CD47-SIRPα “don’t eat me” signaling pathway.29 Finally, all-trans retinoic acid or histone deacetylase inhibitors increase CD38 expression levels, which explains their synergy with CD38-targeting antibodies.30,31

In summary, killing of MM cells by CD38 or SLAMF7 antibodies can be improved by adding conventional anti-MM agents or new immunotherapy drugs. On the basis of these preclinical results, numerous antibody-based combinations are in different phases of clinical testing.

**CURRENT CLINICAL INDICATIONS: ELOTUZUMAB AND DARATUMUMAB**

**Elotuzumab Plus Lenalidomide and Dexamethasone**

Elotuzumab is approved for use in combination with lenalidomide and dexamethasone for patients with relapsed MM who have received at least one prior line of therapy. The approval was based on the phase III ELOQUENT 2 trial, in which 646 patients who had received one to three prior lines of therapy received lenalidomide and dexamethasone with or without elotuzumab.32 The addition of elotuzumab to lenalidomide and dexamethasone improved the rate of overall response (79% vs. 66%; p < .001) and extended median progression-free survival, the primary endpoint of the study, by 4.5 months (19.4 vs. 14.9 months; hazard ratio, 0.7; p < .001). There was a modest increase in severe adverse events associated with the three-drug regimen (65% vs. 57%). Infusion reactions occurred in 10% of patients who received elotuzumab and were typically low grade in terms of severity.

**Daratumumab Monotherapy**

Daratumumab initially received accelerated approval as monotherapy for patients with three or more prior lines of...
treatment on the basis of data from the phase I GEN501 trial and the phase II SIRIUS trial. The GEN501 trial included a 32-patient dose escalation component and a 72-patient dose expansion component. Among patients treated in the dose-expansion component at doses of 16 mg/kg, who had received a median of four prior lines of therapy, the overall response rate was 36% and the progression-free survival was 5.6 months.

In the SIRIUS trial, 106 patients whose disease was refractory to both an immunomodulatory agent and proteasome inhibitor received 16 mg/kg of daratumumab. The overall response rate was 29%; 34% of patients experienced clinical benefit, defined as a minimal response or better. The median progression-free survival was 3.7 months, and the overall survival rate at 12 months was 64.8%.

The most frequent high-grade toxicities in these two studies were anemia, neutropenia, and thrombocytopenia. Infusion reactions were noted in 71% of patients in GEN501 and in 42% of patients in SIRIUS, the majority of which occurred during the first two infusions and were grade 1 or 2 in severity.

**Daratumumab Combination Regimens**

As discussed previously, preclinical models suggested that daratumumab enhanced the antitumor effects of immunomodulatory agents and proteasome inhibition. Indeed, this observation was confirmed in the phase III CASTOR and POLLUX trials. In CASTOR, 498 patients previously treated with at least one line of therapy received either bortezomib and dexamethasone or daratumumab plus bortezomib and dexamethasone. The addition of daratumumab led to substantial improvement in rates of overall response (82.9% vs. 63.2%; p < .001), very good partial response or better (59.2% vs. 29.1%; p < .001), and complete response (19.2% vs. 9.0%; p = .001). The use of daratumumab was associated with significant benefit in terms of progression-free survival, the primary endpoint of the study (median not reached vs. 12.1 months; hazard ratio, 0.39; p < .001). Anemia, neutropenia, and thrombocytopenia were more common among patients who received daratumumab, as were diarrhea, upper respiratory infection, cough, dyspnea, and peripheral edema. Infusion reactions occurred in 45% of patients who received daratumumab. The results of CASTOR led to approval of daratumumab plus bortezomib and dexamethasone in patients who have received at least one prior line of therapy.

In POLLUX, 569 patients who had previously received at least one line of therapy were treated with lenalidomide and dexamethasone with or without daratumumab. The addition of daratumumab to lenalidomide and dexamethasone led to striking improvement in rates of overall response (93% vs. 76%; p < .0001) and complete response or better (43% vs. 19%; p < .0001). The rate of minimal residual disease negativity at a level of tumor cell detection of 1 × 10⁻⁵ white cells also was substantially higher in patients who received daratumumab (22.4% vs. 4.6%). These higher rates of response translated in turn to superior 12-month progression-free survival (83.2% vs. 60.1%) and a hazard ratio for disease progression or death of 0.37. Diarrhea, neutropenia, upper respiratory infection, and cough were more common in patients who received daratumumab. The results of POLLUX led to approval of daratumumab plus lenalidomide and dexamethasone in patients who have received at least one prior line of therapy.

Daratumumab was recently approved for use in combination with pomalidomide and dexamethasone for patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor, on the basis of results of the phase I EQUULEUS trial. Among 103 patients who had median of four prior lines of therapy, 71% of whom with disease refractory to proteasome inhibitor and immunomodulatory drug, the rate of overall response was 60%, that of very good partial response or better was 42%, and that of complete response or better was 17%. The median progression-free survival was 8.8 months, and the 12-month progression-free survival rate was 42%. Infusion reactions occurred almost exclusively during the first infusion and affected 50% of patients. The most common grades 3 and 4 treatment-related adverse events were hematologic: anemia (28%), leukopenia (24%), neutropenia (77%), and thrombocytopenia (19%).

**MONOCLONAL ANTIBODIES IN THE OVERALL MANAGEMENT OF MULTIPLE MYELOMA**

Initial Management of Multiple Myeloma

After the diagnosis of multiple myeloma is made, most patients will be treated, according to the new SLIMCRAB criteria, with both a proteasome inhibitor and an immunomodulatory drug along with corticosteroids. This approach has been established on the basis of multiple phase III trials that have validated the combination of these two novel classes of drugs. In two of these trials, the response rate was augmented by approximately 10% when a proteasome inhibitor and immunomodulatory drug were combined, which translated into a large difference in progression-free survival. Importantly, the second trial, SWOG777, was conducted in patients who were eligible and ineligible for transplantation, which thus unified treatment strategies for both groups, independent of transplantation status. In more frail patients, however, the combination of lenalidomide and dexamethasone is used more often, on the basis of results of the FIRST trial.

The role of autologous stem transplantation in patients was reinforced recently in a large phase III trial that compared bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance to this combination plus immediate stem cell transplantation followed by lenalidomide maintenance. The group that underwent transplantation had a higher response rate and improved progression-free survival, but there was no difference in overall survival. Maintenance therapy often is used among patients who undergo transplantation and among those who do not.
Post-transplantation maintenance therapy with lenalidomide has been approved by the U.S. Food and Drug Administration on the basis of two randomized, placebo-controlled phase III trials that demonstrated great benefit in progression-free survival and—in one trial—an overall survival advantage.43

DETERMINANTS OF CHOICE OF THERAPY IN RELAPSED MYELOMA

As previously noted, the choice of induction therapy for patients with newly diagnosed MM has been streamlined by recent clinical trial data that highlight the benefit of three-drug combinations that incorporate a proteasome inhibitor and immunomodulatory agent. In contrast, there is a large and growing number of treatment options for patients with relapsed disease. With multiple options now available, including the antibody-based triplets discussed in the previous section, it is becoming increasingly difficult for the clinician to select the best relapse therapy for a patient. Treatment choice has become a rather complex decision-making process that must be based on multiple factors.44 It is no longer a simple sequential algorithm but is dependent on several patient-, disease-, and treatment-related factors. These include the following:

1. Consideration of previous therapies: For an incurable illness, re-treatment can help control the disease. If a previous therapy has worked (usually defined by a partial response that lasts at least 6 months), it can be reconsidered.

2. Current maintenance therapy: With the prolific use of maintenance therapy, especially lenalidomide, relapsed disease usually would be treated with a regimen that does not contain the maintenance therapy agent.

3. The rate of relapse: Patients with aggressively relapsing disease, who often are at high risk and have rapidly growing disease, should be treated with more aggressive combinations. Conversely, patients with slow and indolent disease may be able to have their disease controlled with milder combination therapy.

4. Frailty and comorbidities: These are underappreciated factors in myeloma and are critical, especially because most patients with relapsed disease are older than age 70. These factors in to both the choice of agents and dosage used. Indeed, nearly all agents in myeloma, especially corticosteroids, can have doses adjusted for frailty and comorbidity.

5. Drug availability and convenience: With complex insurance arrangements and costly drugs, the impact of drug cost, or what has been referred to as "financial toxicity," on the patient should be considered and discussed.

6. Clonal evolution: There is increasing evidence that, in high-risk patients in particular, the disease may evolve over time with emergence of a dominant tumor clone. This may influence therapy to potentially re-use prior therapies to which the patient may now be sensitized or to be more aggressive in proliferating disease.

CLINICAL CHALLENGES ASSOCIATED WITH USE OF MONOCLONAL ANTIBODIES IN MULTIPLE MYELOMA

A number of specific clinical challenges are associated with the administration of monoclonal antibodies in MM. Understanding when and how these may occur, and how best to address them when they do, is critical to the effective use of regimens that incorporate daratumumab and elotuzumab.

Infusion Reactions

As noted previously, infusion reactions are frequent with daratumumab (40%–50%) but are less common with elotuzumab (10%). They occur most often during or after the first two infusions and are uncommon thereafter. The symptoms are variable and can include chills, headache, nasal congestion and rhinorrhea, throat irritation, cough, wheezing, dyspnea, nausea, vomiting, and rash. They are typically low grade in severity and resolve when the infusion is held and appropriate interventions are taken. After symptoms resolve, the infusion can resume with the intention of completing the entire infusion on the same day.

With respect to daratumumab, premedications should include a glucocorticoid, such as methylprednisolone or dexamethasone; an antihistamine; and acetaminophen. Montelukast often is given as a premedication during the initial cycle of therapy to reduce the risk of respiratory symptoms, particularly among patients with underlying lung disease. An oral corticosteroid is administered for 2 days after each dose of daratumumab in the initial cycle of treatment to prevent delayed infusion reactions.

With regard to elotuzumab, it is standard to administer oral dexamethasone 3 to 24 hours before the infusion at home and an intravenous dose of dexamethasone along with an antihistamine and acetaminophen immediately before elotuzumab administration.

Blood Typing Interference by Daratumumab

Daratumumab interferes with blood typing by binding to CD38 on reagent blood cells and causing a positive indirect Coombs test.45 Thus, it is important to notify the blood bank at treatment sites about new patients who will receive daratumumab and obtain a type and cross before the first dose. A technique to mitigate daratumumab interference with a reproducible dithiothreitol-based method has been developed46 and may be broadly available to treatment sites.

Fortunately, transfusion reactions such as hemolysis in daratumumab-treated patients have been rare despite the great need for transfusion support in patients with relapsed myeloma in particular. This was underscored by the experience of patients in the SIRIUS trial: despite the red blood cell transfusion rate of 38% and platelet transfusion rate of 14%, there was only one transfusion-related event, a platelet transfusion reaction.47

Infection Risk

As demonstrated in the GEN501, SIRIUS, and subsequent trials, daratumumab causes a moderate degree of bone
marrow suppression, including leukopenia, neutropenia, and thrombocytopenia. As a result of this and other effects of the agent on immunity, use of daratumumab is associated with increased risk of infection. The concomitant use of corticosteroid premedication undoubtedly increases this risk as well.

The impact of this infection risk was demonstrated by toxicity data from the CASTOR and POLLUX trials, which showed a higher rate of all-grade upper respiratory infections in patients treated with daratumumab compared with those in the control group (24.7% vs. 18% in CASTOR and 31.8% vs. 20.6% in POLLUX).35,36 However, longer treatment exposure in the daratumumab arms also may have contributed to the increased infection frequency.

Elotuzumab is less marrow suppressive than daratumumab, and, in the ELOQUENT 2 trial, the rates of anemia, thrombocytopenia, and neutropenia were similar in the investigational and control groups.32 There was, however, a significantly higher rate of grades 3 and 4 lymphocytopenia in the investigational group (77% vs. 49%). Moreover, patients who received elotuzumab, like those who received daratumumab, also received substantial doses of corticosteroid; the need for coadministration of a corticosteroid thus implies an increased risk of infectious events associated with the use of elotuzumab as well.

Use of prophylactic antibiotics is recommended for patients who receive either daratumumab or elotuzumab. This prophylaxis should include an antiviral drug, such as acyclovir or valacyclovir, and an agent to prevent Pneumocystis carinii pneumonia, such as sulfamethoxazole/trimethoprim or dapsone.

Single-Agent Versus Combination Therapy
As trials continue to demonstrate the superiority of combinations versus single agents in myeloma, it may be unclear to the clinician when daratumumab may be used as a single agent. Although it is more likely to be used in combinations with lenalidomide, bortezomib, pomalidomide, and—soon—carfilzomib, the single-agent activity and tolerability of the drug also allows its use alone. This type of use is most likely for frail patients who may not tolerate drug combinations, for more indolent disease that requires less-aggressive therapy, or for multi-refractory disease in which no other options exist. The role of single-agent daratumumab in maintenance therapy is attractive by virtue of its long half-life, single-agent activity, and experience with monoclonal antibody therapy maintenance in other diseases; however, single-agent use must be validated in prospective trials. Also, increasing evidence suggests synergy with daratumumab when used in combination with immunomodulatory drugs that could overcome resistance to both drugs.48 This possibility may have implications toward the re-use of daratumumab in patients whose disease was previously resistant to the drug.

OTHER COMBINATIONS OF Daratumumab and Elotuzumab
On the basis of the promising data presented here, a number of ongoing studies are exploring the role of daratumumab and elotuzumab either as single agents or in combination outside of the setting of relapsed disease. Examples include use as induction therapy for newly diagnosed patients (e.g., daratumumab-VRD, daratumumab-MPV, elotuzumab-VRD), as maintenance treatment (either as single agent or in combination) after autologous transplantation, or in combinations with other agents in the relapsed setting. Early reports suggest no major additive adverse effects or toxicities, and outcome data are eagerly awaited.49,53 Because of the success of the antibodies in MM, antibodies now are being explored in other plasma cell dyscrasias, also; daratumumab has shown promising results in patients with amyloid.54

OTHER CD38- and SLAMF7-TARGETING ANTIBODIES
Besides daratumumab and elotuzumab, other CD38- and SLAMF7-targeting molecules are in clinical development. Importantly, in vitro studies show that these molecules rely on different mechanisms of action (e.g., ADCC, ADPC, CDC) and so may play a role in MM therapy. Examples include isatuximab (SAR650984) and MOR202, which target CD38,55,57 and ABBV-838, which targets SLAMF7.58

OTHER MYELOMA-TARGETING ANTIBODIES
Data on the use of checkpoint inhibitors in MM are contradictory. Initial studies suggested that anti–PD-1 and anti–PD-L1 agents were highly effective in combination with traditional therapy in the relapsed setting (e.g., lenalidomide, pomalidomide, bortezomib).59,61 Recently, however, the phase III studies were placed on a temporary hold as a toxicity signal was investigated. These studies have been modified and reopened; results are awaited.

Clinical studies are underway to investigate a number of antibodies to other MM surface targets, both alone (naked) or with the addition of an immunotoxin. Antibodies (e.g., GSK2857916) to target the B-cell maturation antigen, which is highly expressed on MM cells, show promise.62 Others include the anti–CD40 lucatumab; the anti–CD138 immunotoxin indatuximab ravtansine; the anti–CD56 immunotoxin lorvotuzumab mertansine; and PAT-SM6, which targets the heat shock protein glucose-regulated protein 78.63,66

CHIMERIC ANTIGEN RECEPTOR T CELL AND BISPECIFIC ANTIBODY APPROACHES
In addition to antibody-based therapies, a number of other approaches to harness the patient’s own immune system are being explored. The most advanced approaches include T cells that are redirected to targeting tumor surface antigens by chimeric antigen receptors (CAR) and bispecific antibody constructs that target both the tumor and T cell. After the incredible responses to CAR T-cell therapy in patients with acute leukemia and lymphoma, similar approaches are being explored in multiple myeloma. Although responses to CD19–directed CAR T cells have been reported in myeloma,67 the experience with B-cell maturation antigen–directed CAR T cells is impressive.68,69 Despite the infrastructure requirements for such an approach (i.e., cell apheresis,}
in vitro transfection and expansion, shipping, and—finally—reinfusion of the CAR T-cell product, studies to date show that products can be made for patients and can induce high response rates, including complete responses. As with other CAR T-cell therapies, the management of adverse effects, especially cytokine release syndrome, which is unpredictable both in severity and timing, is important. Other T-cell targets under investigation include κ light chain, CD38, and SLAMF7. An alternate approach to redirecting T cells to tumors is achieved with bispecific antibodies. As one fragment binds to the tumor surface antigen, another simultaneously engages T cells via CD3. In contrast to CAR T cells, the products are not patient specific and so may be considered off the shelf. Again, such an approach has shown great promise in CD19+ acute lymphoblastic leukemia, for which blinatumomab is approved. In myeloma, ongoing phase I studies are looking at CD3/B-cell maturation antigen/CD3 and other targets (e.g., CD38 and CD138). As with CAR T cell approaches, cytokine release syndrome can occur.

**CONCLUSION**

The past 5 years have seen a revolution in MM therapy as monoclonal antibodies have been incorporated into standard treatment approaches. Clinical studies demonstrate their effectiveness as single agents (daratumumab) and in combination (daratumumab or elotuzumab in combination with proteasome inhibitors and immunomodulatory drugs), and ongoing studies are exploring their use in all stages of disease and in other related plasma cell dyscrasias. Other monoclonal antibodies (both naked and with immunotoxins), as well as bispecific antibodies and CAR T cells, are being explored as the search for the best MM immunotherapy approach continues. Importantly, these approaches exert their tumor control in a way that differs from standard MM treatment; thus, in many cases, the approaches are complementary to the approved standard therapies.

**References**


expression on multiple myeloma cells by all-trans retinoic acid


Risk Stratification and Targets in Multiple Myeloma: From Genomics to the Bedside

Aurore Perrot, MD, PhD, Jill Corre, PharmD, PhD, and Hervé Avet-Loiseau, MD, PhD

OVERVIEW

In the past 15 years, significant improvements in overall survival have been observed in multiple myeloma (MM), mainly due to the availability of novel drugs with variable mechanisms of action. However, these improvements do not benefit all patients, and some of them, defined as high risk, still display short survival. The most important risk factors are the genetic abnormalities present in the malignant plasma cells. The most important high-risk features are the del(17p), the del(1p32), the t(4;14), and 1q gains. Assessing these markers is mandatory at diagnosis and at least at first relapse, since it has been clearly shown that the lenalidomide-dexamethasone combination is not efficient in these high-risk patients. In contrast, a triplet combination adding a proteasome inhibitor or a monoclonal antibody to the lenalidomide-dexamethasone backbone clearly improves the survival. Another way to improve the outcome would be to specifically target genetic abnormalities with specific inhibitors. The sequencing of more than 1,000 MM exomes revealed again a huge heterogeneity. The most frequent mutations involve the KRAS and NRAS genes (20%–25% each). However, to date, no good RAS-inhibitors are clinically available, preventing targeted therapy. The only druggable target is the V600E BRAF mutation. Unfortunately, this specific mutation is present in only 3% of the patients. Finally, it has been recently reported a specific efficiency of the BCL2-inhibitor venetoclax in patients with the t(11;14) translocation, which is found in 20% of the patients.

MULTIPLE MYELOMA

Multiple myeloma is a heterogeneous disease. From a clinical point of view, patients have a highly variable outcome, with survival ranging from a few weeks to more than 15 years, or even cure, especially in transplant-eligible patients. For a long time, treatment strategies did not take into account this survival heterogeneity, which could be predicted on the basis of several prognostic parameters. The main reason was the availability of drugs. However, recently, the demonstration that some combinations may lead to different outcomes, both in high-risk and standard-risk patients, is changing this paradigm.

What are the most important prognostic factors in MM, and how do they predict outcome? MM is probably the cancer for which the most prognostic parameters have been described. They can be categorized into three groups: (1) related to patients, (2) related to disease burden, and (3) related to the malignant clone itself. In the first category, age is probably the most important; it defines the treatment strategy available for these patients, mostly the feasibility of transplant. The age cutoff is usually fixed between ages 65 to 70, depending on the patient’s fitness. Another important factor in this category is the presence or lack of comorbidities, which could prevent the use of some drugs. In the second category (tumor burden), several parameters have been described, such as β2-microglobulin level, serum lactate dehydrogenase level, anemia, thrombocytopenia, and several circulating factors (such as CD138 and GDF15). The International Staging System is based on β2-microglobulin and albumin; the latter reflects several parameters related to the patient’s conditions. Finally, the third category concerns several factors related to the clone biology, such as genetic abnormalities, proliferation index, and the monoclonal protein structure that could lead to renal precipitation or amyloidosis deposit.

GENETIC ABNORMALITIES

If age, comorbidities, renal failure, or amyloidosis will lead to treatment adaptation, the most powerful prognostic factor is related to genetic abnormalities present in the malignant plasma cells. Several abnormalities have been related to prognosis, and all of them are actually predictive of short-term outcome; no abnormalities predicting long-term survival have yet been identified (Table 1). Among these high-risk chromosomal changes, the most powerful is undoubtedly deletion 17p [del(17p)]. Even though this abnormality is recognized as a high-risk factor by all the investigators, some debates are still ongoing. The first one addresses the question of the molecular target of this
deletion. Most investigators focus their analysis on TP53. If this gene is obviously within the minimal deleted region on 17p, several pieces of knowledge are disturbing. The most important one is related to the tumor suppressor function of TP53. In about half of solid tumors, this gene is mutated, leading to dominant negative alteration of its tumor suppressor role. In MM, sequencing analyses showed that the remaining TP53 allele is mutated in only 30% to 40% of the patients.7,16,17 In these patients, TP53 is clearly the target. However, in the remaining 60% to 70% of patients lacking the mutation, it is rather unlikely that this gene is the target, the deletion leading only to a small decrease in TP53 messenger RNA expression (personal data). A recent study in mouse models for acute leukemias or lymphomas did identify other genes in the TP53 vicinity whose deletion was associated with higher aggressiveness.15 Their potential role in MM has to be demonstrated. Some (but not all) studies suggested that the “double hit” TP53 inactivation was associated with a poorer outcome. With the development of next-generation sequencing (NGS) approaches in the risk assessment, this issue should be resolved in the near future.

The second ongoing debate is related on the clone size importance in the prognostic value. The Intergroupe Francophone du Myélome (IFM) did publish more than 10 years ago that the prognostic value of the del(17p) was observed only if the deleted clone size were greater than 60%.7 No other group addressed this issue, leading to confusing data on the role of novel therapies in overcoming this prognostic impact; some investigators defined del(17p) if it was detected in even 1% of the plasma cells.3 To definitively resolve this question, we performed a patient-level meta-analysis of European data including more than 1,000 patients with del(17p) at all the levels. This study confirmed the IFM data, with a cutoff at the 55% to 60% level (manuscript in preparation). With this cutoff, the frequency of del(17p) is 7% to 8% of patients.

The second chromosomal change identified to predict poor outcome is the t(4;14) translocation.7,16,17 Observed in 12% to 15% of the patients, this translocation is unique within the 14q32 translocations observed in B-cell malignancies. First, it is MM specific. Second, it is the only one shown to deregulate two genes located at 4p16: FGFR3 and MMSET. Third, it is the only case showing a fusion gene, Eμ-MMSET. Even though upregulation of FGFR3 leads to oncogenesis in several tumor models, it is probably not the primary oncogenic target in MM. The main reason for this assessment is the observation that FGFR3 is lost in about one third of patients with t(4;14) because of an unbalanced translocation.18 MMSET has methyl-transferase properties, leading to changes in chromatin conformation and deregulation of chromatin accessibility. However, the detailed phenotypic changes of its activation are not yet identified. Even though t(4;14) has been associated with a poor outcome in several studies, its prognostic value has been challenged in several other publications. The first studies arguing for this prognostic value were the demonstration of the activity of proteasome inhibitors in these patients.19,20 Second, the IFM did demonstrate that the prognostic value of t(4;14) must be interpreted more globally in the context of other chromosomal abnormalities, some of which overcome the poor prognostic value (trisomy 5) and others worsening its impact [1q gains, del(1p32)].21 Thus, t(4;14) by itself should not longer be considered a high-risk feature; its interpretation should be with other abnormalities.

The third abnormality associated with a poor outcome is the deletion of the 1p32 region, targeting two genes: FAF1 and/or CDKN2C. Which one of these two genes is the primary target of the deletion is unknown. Few studies have analyzed the prognostic value of this abnormality. In the first IFM publication,22 del(1p32) was observed in 7% to 8% of the patients and presented almost the same prognostic value as did del(17p). On the basis of these data, we believe that this abnormality should be included in the prognostic panel assessed in routine practice.

The fourth abnormality associated with high risk is the 1q gain. This abnormality, observed in one third of the patients, is not MM specific but rather is observed in many cancers. Its molecular targets are unknown, even though many investigators have focused their analyses on the CKS1B gene at 1q21, based on a single old publication.23 More recent studies identified other putative targets, but no clear demonstration of a single target has been convincingly proposed, probably because 1q is a large chromosomal region, rich in genes. The real prognostic value of these 1q gains is a subject of debate. Because of the frequency of this chromosomal abnormality, it cannot be a strong prognostic parameter.24 Some investigators are suggesting that the number of 1q copies may have a role, and that high-risk patients are

**PRACTICAL APPLICATIONS**

- Patients with multiple myeloma present a highly variable survival, mainly driven by genetic abnormalities.
- The del(17p), del(1p32), t(4;14), and 1q gains are the most important high-risk abnormalities.
- In these high-risk patients, a triplet combination of drugs is the most appropriate choice.
- Except the V600E BRAF mutation (present in 3% of patients), no other currently druggable mutation is present in myeloma.
- The BCL2-inhibitor venetoclax seems to be very efficient in patients with the t(11;14) translocation (20% of the patients).

**TABLE 1. Prognostic Value of the Most Frequent Chromosomal Abnormalities**

<table>
<thead>
<tr>
<th>Genetic Abnormalities</th>
<th>Prognostic Value</th>
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<tbody>
<tr>
<td>Del(17p)</td>
<td>High risk</td>
</tr>
<tr>
<td>Del(1p32)</td>
<td>High risk</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>1q gain</td>
<td>Intermediate risk</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Neutral</td>
</tr>
</tbody>
</table>
those with more than three copies. This must be confirmed in prospective series.

Finally, other rare abnormalities have been reported to worsen the outcome, such as the t(14;16) and t(14;20) translocations, targeting MAF oncogene family members. However, these translocations are rare (3% and < 1%, respectively); this makes their prognostic value difficult to establish, even though the t(14;16) is part of the revised International Staging System prognostic model published by the International Myeloma Working Group.25

We believe that the prognostic assessment should be interpreted on a multiparametric basis. To address this issue, we conducted a multivariate analysis of a large cohort of patients (> 1,200) analyzed by single-nucleotide polymorphism arrays, which can identify all copy number changes (manuscript submitted). On the basis of this analysis, we identified five abnormalities associated with a shorter survival—del(17p), del(1p32), 1q gain, t(4;14), and trisomy 21—and only one protective abnormality, trisomy 5. On the basis of multivariate statistical analyses, we described a model in which each variable was associated with a specific prognostic value (manuscript in preparation). Of note, this prognostic model has been established according to a series of patients treated 12 to 15 years ago in order to have sufficiently long follow-up to identify potential good-risk factors. With this algorithm, we identified a group of 15% of patients with a median overall survival of 2 years. These data were then confirmed in two independent large series of patients treated during the same period. However, note that prognostic models are valid only with a specific therapeutic approach. For instance, our model was mainly built on transplant-eligible patients treated with a vincristine/doxorubicin/dexamethasone or bortezomib/dexamethasone induction, without any consolidation or maintenance phases. To test the stability of our model for patients treated with more modern approaches, we applied it in the IFM2009 trial. These patients received a bortezomib/lenalidomide/dexamethasone induction, high-dose melphalan (for half of them), consolidation, and lenalidomide maintenance. We confirmed its ability to detect three groups of patients, with a significant improvement in the overall survival curves in all three groups.

RISK-ADAPTED THERAPY

In the era of risk-adapted therapy, high-risk patients must be identified so that they are not missed and so that they may receive the most powerful therapeutic combinations. Until recently, all patients were treated with the same approaches, independent of their individual risk. Several phase III trials enrolling relapse/refractory patients addressed the issue of the outcome (mostly progression-free survival) of high-risk patients.2–4 Most of these trials had a common control arm (lenalidomide/dexamethasone), with a lenalidomide-based experimental arm. All these trials, testing novel second-generation proteasome inhibitors (carfilzomib, ixazomib) or monoclonal antibodies (elotuzumab, daratumumab), showed significant improvements in the progression-free survival of high-risk patients. However, all these trials had some caveats, mainly in the definition of the high-risk group. This group was uniformly defined by the presence of del(17p), t(4;14), and/or t(14;16), according to the International Myeloma Working Group recommendations. However, some caution should be taken with the interpretation. For instance, a huge heterogeneity in the definition of del(17p) was observed. Del(17p) was defined by the presence of only one fluorescence in situ hybridization signal in more than 1% of the plasma cells in the elotuzumab trial,3 to 20% in the ixazomib trial,4 to 60% in the carfilzomib trial.5 In the daratumumab trials,26,27 del(17p) was identified by NGS, with no specific cutoff. The second caveat for these data is the definition of high risk. As discussed previously, all these trials took an old monoparametric definition. Because some of these trials evaluated other genetic changes, such as 1q gains, retrospective analyses are feasible to test a multiparametric evaluation of risk.

On the basis of these (imperfect) data, we believe that it is time to recommend specific drug combinations for high-risk patients. Because all these trials were dedicated for relapsed/refractory patients (mostly at first relapse), a triplet combination combining lenalidomide/dexamethasone plus a proteasome inhibitor or a monoclonal antibody is recommended for this high-risk group. This means that risk should be re-evaluated at the time of relapse because the risk category sometimes changes. The next question is whether these results (and thus recommendations) can be extrapolated to the frontline setting. Formally, the answer is no. However, we believe that before the release of frontline studies using the same combinations in the next 12 to 24 months, the same approach should be applied for patients at diagnosis.

TARGETED THERAPY

In the past 3 years, several publications reported on the use of NGS in MM.14,28–30 Most of these studies sequenced the exome of patients in both the diagnostic and the relapsed setting. Once again, these studies confirmed the molecular heterogeneity of MM. No single gene mutation was observed. The most frequently mutated genes are the KRAS and NRAS genes (approximately 25% and 20% of patients, respectively), followed by the DIS3 and FAM46C genes (10%–12% each; Table 2). All the other genes are mutated in less than 10% of patients. A few studies addressed the question of the prognostic value of these mutations. Among the genes observed to be mutated in more than 3% of patients, only TP53 mutations (observed in 6%–8% of patients) showed a detrimental prognostic value. All the other mutations were neutral for prognosis. These data suggest that mutations do not play a major role in the aggressiveness of MM. Some rarer mutations (present in < 3% of the patients) may affect the outcome, positively or negatively, and only much larger prospective studies may answer this question.

Another question resolved by these studies was the mutation load of MM. It has been shown that MM is in the middle range of the human cancers for the mutation load, far from
lowly mutated leukemias but also far from highly mutated carcinogen-induced tumors, such as melanoma and lung cancer.\textsuperscript{31} Because a highly significant correlation has been demonstrated between the mutation load and response to immune checkpoint inhibitors (through a probable neoantigen formation),\textsuperscript{32} it is unlikely that this approach will be successful in MM; this hypothesis has been confirmed by preliminary studies.

Among the many mutations observed in MM, are some of them targeted by specific inhibitors? This approach is widespread in solid tumors but has never been widely used in hematologic malignancies. In MM, few mutations appear to be druggable. The most evident ones are the \textit{BRAF} mutations. A single paper,\textsuperscript{33} reporting a single patient, addressed this issue. Investigators treated a patient with advanced disease (including extramedullary localization) with vemurafenib, a \textit{BRAF} inhibitor. After 1 month of single-agent treatment, the patient presented a dramatic response, with normalization of the monoclonal component and substantial shrinkage of the extramedullary localization. This patient harbored a clonal \textit{BRAF} V600E mutation, known to constitutively activate \textit{BRAF} kinase activity. No other report or trial testing this approach has been published.

Several reasons may explain this lack of data. First, even though \textit{BRAF} mutations are among the most frequently observed in MM, they are found in only 5% to 8% of patients. Second, these mutations have to activate \textit{BRAF}. The V600E mutation represents only a subset of these mutations, probably about half of them. Third, to be really druggable, these mutations have to be fully clonal. The analysis of the published exome data reveals that it is not the case in a large number of patients, many of them displaying the mutation only in subclones. The use of a \textit{BRAF} inhibitor in such patients would lead to only a partial response at best. These data are surprising because \textit{BRAF} is supposed to be a driver in oncogenesis. However, at least in MM, it has been shown that mitogen-activated protein kinase pathway activation may be due to subclonal mutations of \textit{NRAS}, \textit{KRAS}, and/or \textit{BRAF} but or to mutations of two of these genes.

The second mutations that can be targeted are the \textit{RAS} mutations, either \textit{KRAS} or \textit{NRAS}. These mutations usually lead to activation of the MAP kinase-ERK kinase (MEK) pathway.

**TABLE 2. Frequency and Clinical Value of the Mutations Most Frequently Observed in Multiple Myeloma**

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Frequency (%)</th>
<th>Prognostic/Therapeutic Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{KRAS}</td>
<td>20–25</td>
<td>MEK inhibitors</td>
</tr>
<tr>
<td>\textit{NRAS}</td>
<td>20</td>
<td>MEK inhibitors</td>
</tr>
<tr>
<td>\textit{DIS3}</td>
<td>10–12</td>
<td></td>
</tr>
<tr>
<td>\textit{FAM46C}</td>
<td>10–12</td>
<td></td>
</tr>
<tr>
<td>\textit{TP53}</td>
<td>6–10</td>
<td>Poor prognosis</td>
</tr>
<tr>
<td>\textit{BRAF}</td>
<td>3–6</td>
<td>\textit{BRAF} or MEK inhibitors</td>
</tr>
</tbody>
</table>

Abbreviations: MEK, MAP kinase-ERK kinase; \textit{BRAF}, B-Raf proto-oncogene.

Again, few papers reported on the use of MEK inhibitors in such patients, with disappointing results.\textsuperscript{36–37} Thus, it is unlikely that targeted treatment based on mutations will have real promise in MM.

Finally, a recent publication reported on the high activity of a B-cell lymphoma 2 inhibitor, venetoclax, in patients harboring the t(11;14) translocation (40% objective responses in a single-agent trial).\textsuperscript{38} The reasons for this high efficiency are not clear. The authors did propose that a high B-cell lymphoma 2/myeloid cell leukemia 1 messenger RNA ratio correlated with response. However, in our patients, patients with t(11;14) did not present a high ratio (unpublished data).

**MINIMAL RESIDUAL DISEASE**

If NGS data gave relatively disappointing results on the role of mutations in risk stratification or for targeted therapy, they show that the mutations may have another application in the assessment of minimal residual disease (MRD). As in several hematologic malignancies, MRD accurately predicted outcome in MM. Use of NGS targeting the immunoglobulin gene rearrangements showed that MRD could be quantified with a high sensitivity (one plasma cell in 1 million bone marrow cells, or \(10^{-6}\)).\textsuperscript{39} A recent meeting report showed that MRD negativity established with use of this cutoff predicted significantly different progression-free survival and overall survival. It also showed that the type of treatment does not really matter if patients have chemotherapy-sensitive disease and achieve MRD negativity. Finally, it showed that chemotherapy sensitivity leading to MRD negativity overcame the cytogenetic risk, at least for progression-free survival. MRD will probably become the primary endpoint for prospective trials in the future. Another probable use of MRD in the near future will be the adaptation of treatment based on MRD results. Of course, this attitude will require prospective trials, but it is likely that maintenance or maintenance duration could be adapted on the basis of these results.

Another way (complementary to molecular or cellular assessment) to evaluate MRD is the use of imaging techniques, the most powerful being PET in tandem with tomodensitometry or PET-MRI.\textsuperscript{40} This technique can detect residual metabolically active focal lesions. Depending on the number and localization of these residual lesions, targeted therapy, such as focal external radiotherapy or tomotherapy, could be used to sterilize these lesions. Currently, detection is based on the tumor cell avidity for glucose, but several other, more specific compounds are being evaluated. Thus, more specific and, moreover, more sensitive techniques will probably lead to better detection of MRD.

**CONCLUSION**

In the past 3 years, many patient samples have been sequenced, leading to a clear picture of the mutational landscape in MM. Once again, these studies showed a huge heterogeneity at the molecular level, failing to identify clear pathophysiologic subentities and important molecular druggable targets. This does not mean that sequencing
should be abandoned; it still has clear routine applications, such as risk assessment in a single technique (evaluating at the same time copy number changes, 14q32 translocations, and TP53 mutations) or MRD evaluation. Clearly, risk evaluation is mandatory, both at diagnosis and relapse, to select the most appropriate combinations of therapy.

References


Despite advances in therapy, myeloma remains incurable in most patients. Outcomes remain particularly poor for those with adverse cytogenetics or disease that has become resistant to multiple lines of therapy. Novel approaches are needed for these populations. Immunologic-based therapies, such as vaccines, immunomodulating antibodies, and cellular therapies, have a unique mechanism of action that may overcome drug resistance and, particularly for cellular therapies, potentially provide long-term tumor surveillance and durable disease control. However, widespread clinical application of immune-based approaches for myeloma has been limited by toxicity (e.g., for allogeneic stem cell transplantation [SCT], PD-1 inhibitors) or poor/inconsistent efficacy (e.g., for tumor vaccines). In 2018, that narrative may be changing because of cellular therapies. Cellular therapies fall into two broad categories: (1) non–gene-modified strategies, which rely on the endogenous anti-myeloma T-cell repertoire, and gene-modified strategies, which introduce a new T-cell receptor (TCR) or a chimeric antigen receptor (CAR) to confer novel antigen specificity. CAR T cells show the greatest activity to date. Multiple antigen targets, including B-cell maturation antigen (BCMA), CD19, CD38, CD138, and SLAMF7, are being explored for myeloma, and BCMA has emerged as the most promising. Preliminary data from four phase I studies of BCMA CAR T cells, each using a different CAR construct, that involved 90 evaluable patients with relapsed/refractory disease have been reported. These data show response rates of 60% to 100%, including minimal residual disease (MRD)-negative complete remissions, at effective doses (> 10^8 CAR-positive cells) after lymphodepleting conditioning. Response durability has been more variable, likely related to differences in CAR T-cell products, lymphodepleting regimens, patient selection criteria, and/or underlying biology/prognostic factors. In the two most recent studies, however, most patients remained progression free with median follow-up time of 6 to 10 months; some ongoing remissions lasted more than 1 year. Toxicities are similar to those from CD19 CAR T cells and include cytokine release syndrome and neurotoxicity that is reversible but can be severe. Multiple BCMA CAR T-cell studies are ongoing. Future directions include combinations with immunomodulatory drugs, checkpoint inhibitors, or other CAR T cells, as well as use of gene-edited cellular products to enhance the safety and efficacy of this approach.
(e.g., T cell–depleted stem cell grafts, post-transplantation cyclophosphamide),\textsuperscript{11,12} antigen-specific donor lymphocyte infusions,\textsuperscript{13} and/or novel conditioning and maintenance regimens (e.g., incorporation of proteasome inhibitors).\textsuperscript{14}

Another non–gene-modified approach has been the use of autologous lymphocyte infusions (ALIs) as an adjunct to high-dose melphalan and autologous SCT, often in conjunction with a tumor vaccine. The rationale for this approach is to take advantage of the reconstituting immune milieu after autologous SCT to facilitate induction of an antimalleoma immune response.\textsuperscript{15} A priming dose of the vaccine is given before collection of autologous peripheral blood lymphocytes; collected cells then are reinfused within the first 2 weeks after autologous SCT, either as an unmanipulated autologous lymphocyte infusion product or after ex vivo expansion and activation of T cells by using anti–CD3/CD28 beads. This is then followed by several booster doses of vaccine. Several studies have demonstrated the feasibility, safety, and immunogenicity of this approach, with induction of humoral and cellular immunity against both infectious antigens (e.g., influenza) and myeloma tumor antigens (e.g., hTERT [telomerase reverse transcriptase], survivin, MAGE-A3).\textsuperscript{5,6,16,17}

However, the clinical impact of the autologous lymphocyte infusion and vaccine combination approach has been difficult to discern because of the concomitant administration of high-dose melphalan, and durability of responses in these studies has been disappointing. A specialized form of autologous lymphocyte infusion that uses activated lymphocytes derived from bone marrow, called marrow-infiltrating lymphocytes (MIL), recently showed promising outcomes in a small study that combined MIL with autologous SCT without the use of a tumor vaccine. Marrow-infiltrating lymphocytes were shown to harbor a broader and more effective myeloma-specific T-cell repertoire compared with peripheral-blood lymphocytes, and deeper remissions were noted in the patients with the greatest antimalleoma T-cell responses.\textsuperscript{18} A larger follow-up study to explore this approach is underway (NCT01858558).

**PRACTICAL APPLICATIONS**

- Despite improved outcomes with novel agents, most patients with myeloma eventually develop drug resistance and succumb to their disease.
- Cellular therapies provide the potential to overcome drug resistance and induce durable remissions with a single treatment.
- BCMA-specific CAR T cells have shown promising clinical activity, including a high proportion of complete responses, in patients with highly refractory myeloma.
- BCMA CAR T cells can cause cytokine release syndrome and neurotoxicity, similar to CD19 CAR T cells, without unexpected off-target or off-tumor toxicities noted to date.
- Many CAR T and other cellular therapy trials for myeloma are opening in 2018, which will allow for greater availability of these approaches to patients.

**GENE-MODIFIED T-CELL THERAPIES**

Gene-modified T-cell therapies generally fall into two categories: (1) T cells that express a transgenic T-cell receptor (TCR Tg) that recognizes a traditional antigenic peptide–MHC complex; and (2) T cells that express a CAR that typically uses a single-chain variable fragment (scFv)–based antigen-recognition domain coupled to a T-cell signaling domain (e.g., CD3ζ).\textsuperscript{19} In both cases, autologous (or in some studies, allogeneic) T cells are collected via leukapheresis, transduced with the new receptor, expanded ex vivo during a 2- to 3-week period, and then re-infused into the patient. The primary advantage of the TCR Tg T-cell approach is that any tumor antigen can be targeted, including unique neoantigens or shared antigens that may be expressed only intracellularly, whereas CAR T cells can recognize antigens only on the cell surface. This approach may be especially useful in solid tumors,\textsuperscript{20,21} for which there is a dearth of tumor-specific surface antigens amenable to the CAR approach. The TCR Tg T-cell approach has several disadvantages, however, which include a requirement for a specific HLA type, which limits the applicable patient population; the theoretical potential for recombination with endogenous TCR α or β chains, which leads to unwanted specificity; and the potential for off-tumor toxicity via recognition of an unexpected peptide–MHC complex with homology with the tumor peptide. This homology concern was demonstrated in a trial of autologous T cells that expressed a Tg TCR specific for a MAGE-A3 class I peptide. In the trial, two patients developed fatal cardiotoxicity shortly after T-cell infusion. There was diffuse T-cell infiltration within the myocardium, and it was subsequently shown that the Tg TCR also recognized a peptide derived from the myocardial protein titin.\textsuperscript{22}

In myeloma, TCR Tg T cells restricted to HLA-A0201 and specific for a peptide derived from NY-ESO1 (and its homolog LAGE) are being explored. These cancer-testis antigens are expressed in up to 50% of patients with myeloma, and there is higher expression in relapsed disease.\textsuperscript{23} Clinical activity of these cells has been demonstrated in early-phase studies in sarcoma and melanoma.\textsuperscript{21} Rapoport et al\textsuperscript{24} conducted a pilot study in patients with myeloma who were undergoing upfront or salvage autologous SCT. Of 70 patients screened, 20 were HLA-A0201 positive, had tumors that expressed either NY-ESO1 or LAGE, and were eligible. Patients received a median dose of $2.4 \times 10^7$ TCR Tg T cells on day 2 after high-dose melphalan and autologous SCT. Infusions were well tolerated; self-limited autologous graft-versus-host disease occurred in three patients, and there were no off-target toxicities. Cells expanded in all patients and could be detectable more than a year after infusion in some. Complete or near complete responses were seen in 70%, and the median PFS was 19.1 months. Relapse was associated with either loss of T cells or loss of NY-ESO1/LAGE expression in myeloma cells.\textsuperscript{24} Although this study demonstrated the safety and biologic activity of this approach, it is difficult to interpret the clinical impact of the T cells in this heterogeneous population that also underwent autologous SCT. An ongoing follow-up study in relapsed/refractory myeloma
is exploring the use of these cells without concomitant SCT (NCT03168438) and should provide more information about the efficacy of this approach.

The use of CARs to induce T-cell activation and effector function were first described more than 25 years ago, but the successful translation of this approach to the clinic in the past decade is due to several key advances, namely (1) the incorporation of costimulatory domains, such as CD28 and 4-1BB, into CAR design, to enhance proliferation and survival; (2) the use of modified lentiviral and retroviral vectors to transduce T cells and obtain stable CAR expression; (3) advances in cellular manufacturing and expansion techniques; and (4) the addition of lymphodepleting chemotherapy conditioning before CAR T cell infusion to enhance expansion and persistence. The greatest success to date has been with CD19-directed CAR T cells, with which great activity has been seen in patients with relapsed/refractory acute lymphoblastic leukemia, chronic lymphocytic leukemia, and B-cell non-Hodgkin lymphoma, and which led to the first approvals of CAR T-cell products by the U.S. Food and Drug Administration in 2017.

**CAR T-Cell Toxicities**

The toxicities of CAR T cells include target-specific effects (e.g., depletion of normal B cells with CD19 CAR T cells) as well as nonspecific effects of immune activation, especially cytokine release syndrome (CRS) and neurotoxicity. CRS is associated with rapid expansion and activation of CAR T cells, which leads to highly elevated serum levels of interleukin 6, interferon gamma, and other inflammatory cytokines. This typically occurs in the first 2 weeks, and often in the first few days, after CAR T-cell administration. CRS can have a spectrum of clinical manifestations, which range from mild fevers, malaise, and flu-like symptoms—generally managed just with supportive care—to severe sepsis-like physiology that requires intensive care unit-level care because of persistent high-grade fevers, hypotension, hypoxemia, organ dysfunction, coagulopathy, and pancytopenia. In some cases, CRS is associated with hemophagocytic lymphohistiocytosis/macrophage activation syndrome. CRS can respond to corticosteroids, but this may affect the efficacy of infused CAR T cells. The mainstay of treatment of CRS is interleukin 6 blockade, typically with tocilizumab, an anti–interleukin 6-receptor monoclonal antibody. Treatment of severe CRS with tocilizumab can rapidly abrogate fevers and normalize hemodynamic instability, and tocilizumab does not seem to have a major impact on CAR T-cell expansion and efficacy. A study is underway to explore whether earlier intervention with tocilizumab (e.g., at first sign of fever) may prevent development of severe CRS without compromising efficacy (NCT02906371).

Neurotoxicity also is a common adverse effect of CAR T cells that occurs in 25% to 50% of patients who receive CD19 CAR T cells and generally is concurrent with or shortly after onset of CRS. In most cases, neurotoxicity is self-limiting and low grade and consists of a few days of mild confusion, somnolence, and/or word-finding difficulties; however, it can progress to a CAR T-cell–related encephalopathy syndrome, in which severe manifestations include obtundation, focal deficits, seizures, and (rarely) fatal cerebral edema. The etiology is not as well understood as that of CRS but may involve elevated levels of inflammatory cytokines within the central nervous system, which leads to increased endothelial cell activation and vascular permeability. Patients with higher tumor burden, those with more rapid and severe CRS, and those with underlying neurologic disease may be at higher risk. Management includes treatment of CRS with interleukin 6–directed therapy along with corticosteroids.38

**CAR T Cells for Myeloma**

In myeloma, the largest clinical experience to date has been with CAR T cells that target B-cell maturation antigen (BCMA). However, several other antigen targets, including CD19, kappa light chain, CD38, CD138, and SLAMF7, are being explored also (Table 1).

**BCMA**

BCMA is a cell surface receptor with expression largely limited to late-stage B lineage cells, especially plasma cells. Its ligands are BAFF and APRIL, and its normal function is to maintain long-lived plasma cell homeostasis. BCMA is expressed consistently on multiple myeloma cell lines as well as in primary patient samples, though intensity of expression can vary from patient to patient. BCMA also circulates in the serum in a soluble form (i.e., soluble BCMA), and higher concentrations are associated with immune suppression and poorer clinical outcomes. Ligation of BCMA promotes myeloma cell proliferation, survival, and drug resistance, and antibody-based blockade of BCMA signaling has antymyeloma activity in preclinical models. Thus, BCMA is a rational target for antymyeloma therapy.

Kochenderfer et al at the National Cancer Institute were the first to demonstrate that T cells that express a BCMA-specific CAR could recognize and kill human myeloma cell lines as well as primary myeloma cells from patients. This CAR was derived from a murine anti-BCMA antibody and contained a CD28 costimulatory domain packaged in a gamma-retroviral vector. In vivo studies confirmed activity of BCMA CAR T cells in murine myeloma xenograft studies, which led to a first-in-human study of these cells in patients with relapsed/refractory myeloma. Initially, 12 patients who had a median of seven prior therapies were treated with a single infusion of BCMA CAR T cells at doses that ranged from 0.3 to 9.0 × 10^6 CAR-positive cells/kg, after conditioning with 30 mg/m^2/day of fludarabine and 300 mg/m^2/day of cyclophosphamide for 3 days. Limited activity was seen at the first two dose levels, but three of six patients treated at the highest two dose levels achieved objective responses that lasted from 8 to more than 26 weeks. Responses were associated with CAR T-cell expansion and with typical CAR T-cell toxicities, including CRS, delirium, and pancytopenia, which were most severe at the highest dose level. Of note, to be eligible, patients had to have positive staining for...
BCMA expression in myeloma cells by an in-house immunohistochemistry assay; the authors reported that 62% of bone marrows (52 of 85) screened for the study met these criteria.42 An updated report about this trial was presented at the 2017 American Society of Hematology meeting and described 16 total patients treated at the highest dose level of 9.0 × 10^6 CAR-positive cells/kg.43 Patients had a median of 10 prior lines of therapy; 38% had high-risk

### TABLE 1. Selected CAR T-Cell Targets and Trials for Myeloma*

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Trial Site, Company</th>
<th>Accrual</th>
<th>Identifier/Reference</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCMA</td>
<td>National Cancer Institute</td>
<td>Completed (26 patients)</td>
<td>NCT0221596742,43</td>
<td>First-in-human, CD28 domain, Cy/Flu conditioning; 13 of 16 (81%) ORR at highest dose</td>
</tr>
<tr>
<td></td>
<td>University of Pennsylvania, Novartis</td>
<td>Completed (24 patients' data reported)</td>
<td>NCT0254616744</td>
<td>4-1BB domain; 6 of 10 (60%) ORR at high dose with Cy conditioning</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I, Bluebird</td>
<td>Ongoing (21 patients' data reported)</td>
<td>NCT0265892945</td>
<td>bb2121 construct, 4-1BB domain, Cy/Flu; 17 of 18 (94%) ORR at higher doses</td>
</tr>
<tr>
<td></td>
<td>Multisite phase II, Bluebird</td>
<td>Ongoing</td>
<td>NCT03361748</td>
<td>bb2121 registration study, 94 patients</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I, Bluebird</td>
<td>Ongoing</td>
<td>NCT03274219</td>
<td>bb2121 product (same as bb2121 but enriched for memory T cells)</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I/II, Nanjing Legend</td>
<td>Ongoing (19 patients’ data reported)</td>
<td>NCT0309065946</td>
<td>Binds two BCMA epitopes; Cy conditioning; less-treated population; 19 of 19 (100%) ORR</td>
</tr>
<tr>
<td></td>
<td>Memorial Sloan Kettering/Juno</td>
<td>Ongoing (6 patients’ data reported)</td>
<td>NCT0307032741</td>
<td>2 of 2 responded at higher dose with Cy/Flu; includes cohort with lenalidomide</td>
</tr>
<tr>
<td></td>
<td>Fred Hutchinson, Juno</td>
<td>Ongoing</td>
<td>NCT03338972</td>
<td>Defined CD4/CD8 ratio in final CAR T product</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I/II, Juno</td>
<td>Ongoing</td>
<td>NCT03430011</td>
<td>JCARH125 construct, Flu/Cy</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I, Poseida</td>
<td>Ongoing</td>
<td>NCT03288493</td>
<td>Transposon-based construct**</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I, Kite</td>
<td>Ongoing</td>
<td>NCT03318861</td>
<td>KITE-S85 construct, Flu/Cy</td>
</tr>
<tr>
<td></td>
<td>Multiple hospital sites in China</td>
<td>Ongoing</td>
<td>NCT03322735</td>
<td>Small phase I/pilot studies</td>
</tr>
<tr>
<td></td>
<td>Multisite phase I/II, Autolus Limited</td>
<td>Ongoing</td>
<td>NCT03287804</td>
<td>Novel CAR expressing APRIL to target BCMA and TACI</td>
</tr>
<tr>
<td></td>
<td>Virginia Cancer Specialists, Cartesian Therapeutics</td>
<td>Ongoing</td>
<td>NCT03448978</td>
<td>Product contains CD8+ cells only</td>
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<tr>
<td>CD19</td>
<td>University of Pennsylvania, Novartis</td>
<td>Completed (10 patients)</td>
<td>NCT0213540649,50</td>
<td>CD19 CAR T + salvage autoSCT. Targeting CD19+ myeloma precursor cells.</td>
</tr>
<tr>
<td></td>
<td>Soochow University, China</td>
<td>Ongoing (10 patients reported)</td>
<td>NCT0319641441</td>
<td>CD19 CAR T + BCMA CAR T</td>
</tr>
<tr>
<td></td>
<td>General Hospital of PLA, China</td>
<td>Completed (5 patients)</td>
<td>NCT01886976</td>
<td>Includes pilot of upfront CAR T cells + auto-SCT for high-risk MM</td>
</tr>
<tr>
<td></td>
<td>Soochow University, China</td>
<td>Ongoing</td>
<td>NCT03196414</td>
<td>Combination of CD138 CAR T + BCMA CAR T cells</td>
</tr>
<tr>
<td>Kappa LC</td>
<td>Baylor University</td>
<td>Completed (7 patients with MM)</td>
<td>NCT0088192042</td>
<td>No objective responses</td>
</tr>
<tr>
<td>CD38</td>
<td>Multisite phase I, Sorrento Therapeutics</td>
<td>Ongoing</td>
<td>NCT03464916</td>
<td>To open in 2018</td>
</tr>
<tr>
<td></td>
<td>Shenzhen Geno-Immune Medical Institute, China</td>
<td>Ongoing</td>
<td>NCT03271632</td>
<td>Pilot study testing CAR T cells against multiple antigens</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>Preclinical</td>
<td>NA**2,34</td>
<td>Affinity optimization to limit binding of CAR to CD38 on nonplasma cells</td>
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<tr>
<td>SLAMF7/CS1</td>
<td>NA</td>
<td>Preclinical</td>
<td>NA**5,57</td>
<td>Concern for fratricide; can overcome with gene editing to knock out SLAMF7 in CAR T cells</td>
</tr>
</tbody>
</table>

*Current as of March 2018.

Abbreviations: AutoSCT, autologous stem cell transplantation; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; Cy, cyclophosphamide; Flu, fludarabine; GI, gastrointestinal; LC, light chain; MM, multiple myeloma; NA, not available; ORR, overall response rate.
Cohen et al44 also reported updated data at the 2017 American Society of Hematology meeting about a phase I trial at the University of Pennsylvania to explore BCMA CAR T cells in relapsed/refractory myeloma.44 This study used a different CAR, developed in collaboration with Novartis, that consisted of a fully human anti-BCMA scFv with a 4-1BB costimulatory domain that was packaged in a lentiviral vector. Three cohorts were enrolled sequentially, and the objective was to collect preliminary data about safety, efficacy, and kinetics of expansion both with and without lymphodepleting chemotherapy and at the following higher and lower cell doses: (1) CAR T cells alone at a dose of 1 to 5 × 106 cells; (2) 1.5 g/m2 of cyclophosphamide with 1 to 5 × 107 CAR T cells; and (3) 1.5 g/m2 of cyclophosphamide with 1 to 5 × 108 CAR T cells. CAR T cells were given as split-dose infusions: 10% of the dose was given on day 0, 30%, on day 1; and 60%, on day 2. No prespecified level of BCMA expression on myeloma cells was required for eligibility. As of November 2017, 24 patients (median of seven prior lines of therapy) were evaluable; 96% had high-risk cytogenetics, including 71% with del17p or TP53 mutation, and a median of 70% plasma cells on bone marrow biopsy. In cohort 1 (nine patients), four patients (44%) achieved partial response or better to BCMA CAR T cells alone. In cohort 2, which added cyclophosphamide to a 10-fold lower dose of CAR T cells, only one (20%) of five patients experienced a response, and this cohort was closed early. In cohort 3, incorporation of cyclophosphamide with the higher dose (i.e., 1 to 5 × 109) of CAR T cells led to a disease response in six (60%) of 10 patients. The median duration of response was 4 months, and there were ongoing responses in four patients (range, 3 to 24 months). Cyclophosphamide conditioning was not absolutely required for robust expansion and response, but it did increase the frequency of patients who had strong and durable expansion. Toxicities were similar to those in earlier studies with CAR T cells and included severe CRS in 33% (8 of 24 patients) and severe neurotoxicity in 12.5% (3 of 24 patients). One of these patients had a PRES (posterior reversible encephalopathy syndrome)-like syndrome that resolved after treatment with corticosteroids and cyclophosphamide.44

Berdeja et al45 reported updated data at the 2017 American Society of Hematology meeting about the dose-escalation portion of a third BCMA CAR T-cell trial. This was a multicenter study sponsored by Bluebird Bio, which used a second-generation CAR called bb2121 that contained a murine anti-BCMA scFv (the same one used in the National Cancer Institute trial), a 4-1BB costimulatory domain, and a lentiviral vector. BCMA expression on more than 50% of myeloma cells by immunohistochemistry was required for eligibility. Four dose levels (50, 150, 450, and 800 × 106 CAR T cells) were explored in 21 patients with relapsed/refractory disease (median of seven prior lines of therapy); 43% had high-risk cytogenetics, and 57% had at least 50% plasma cells on bone marrow biopsy. All received fludarabine and cyclophosphamide conditioning before a single CAR T-cell infusion. Responses were seen in 17 (81%) of 21 patients, including 17 (94%) of 18 patients treated at doses of 150 × 106 CAR T cells or higher. Ten patients achieved complete response (seven were confirmed). With a median follow-up time of 40 weeks, only four patients who experienced a response had subsequent progression, and the median progression-free survival was not reached; five patients had ongoing responses for more than 1 year. Toxicity seemed decreased in this study compared with the first two BCMA CAR T-cell trials reported: severe CRS occurred in 10%, and no grade 3 or 4 neurotoxicity occurred during dose escalation (though reversible grade 4 encephalopathy and cerebral edema were observed in one of the first patients treated in the ongoing dose-expansion cohort).45

A fourth BCMA CAR T-cell trial, conducted by Nanjing Legend Biotech in China, reported preliminary results at the 2017 ASCO Annual Meeting.46 This CAR, called LCAR-B38M, uses a novel antigen-binding domain that binds BCMA at two separate epitopes. The costimulatory domain and viral vector used for transduction were not described. BCMA CAR T cells ranging across doses of 0.6 to 7.1 × 106 cells/kg were infused over 3 days after cyclophosphamide conditioning. Patients in this trial were not as heavily pretreated and had a median of three to four prior lines of therapy; specifics of prior therapy and cytogenetics were not described. BCMA expression on myeloma cells by flow cytometry was required for eligibility. At the time of presentation, 35 patients had been treated, and 19 were evaluable for response; 100% of patients experienced a response, including 74% with a complete response. During a median follow-up time of 6 months, no patient with CR had experienced relapse. Toxicity was modest: 83% developed CRS, but only 6% had grade 3 CRS. Tocilizumab was given to 40% of patients, which suggests that earlier administration of this agent during mild CRS may have prevented more severe toxicity. No grade 3 or 4 neurotoxicity was seen.46

In addition to the trials described here, at least 15 other trials of BCMA CAR T cells, including three in combination with other CAR T cells, had opened as of March 2018 (Table 1). Initial data are expected by late 2018 or early 2019.

CD19
Garfall et al49,50 conducted a pilot study to explore the use of CD19 CAR T cells after high-dose melphalan and salvage autologous SCT in relapsed/refractory myeloma on the basis of the hypothesis that the CAR T cells may target a
CD19-positive precursor population with stem cell–like properties that are responsible for drug resistance and relapse. Ten patients who had experienced progression within a year after their initial autologous SCT and had received intervening therapy received a single infusion of 1 to 5 × 10^7 CD19 CAR T cells 12 to 14 days after their second autologous SCT. Infusions were well tolerated, and no notable CRS or neurotoxicity occurred. Two of 10 patients experienced clinical benefit; their remission durations were longer after the second autologous SCT than after their first autologous SCT despite lower doses of melphalan. The low dose of CAR T cells used and the 2-week delay in administration after high-dose melphalan may have limited expansion and clinical impact in this study. Additional studies are investigating the combination of CD19-specific and BCMA-specific CAR T cells; in one small pilot study, no notable increase in toxicity was noted to date. Additional correlative analyses are ongoing and will be important to determine which patients may be likely to benefit from this approach.

**Kappa Light Chain**

Ramos et al explored the use of CAR T cells to target immunoglobulin kappa light chain in patients with B-cell malignancies, including seven patients with kappa-restricted myeloma. Patients received 0.9 to 1.9 × 10^8 CAR-positive cells/m², either alone (if they had received chemotherapy in the past 4 weeks) or after cyclophosphamide lymphodepletion. No objective responses were seen; four patients who had non-progressing but measurable disease after prior autologous SCT or chemotherapy had ongoing stable disease after CAR T-cell infusion lasting 6 weeks to 24 months.

**CD138**

CD138 (syndecan-1) is a cell surface marker expressed on normal and malignant plasma cells. However, it also is expressed to a lesser degree on normal and malignant epithelial cells, which raises concerns about potential off-tumor toxicities from CAR T cells that target this antigen. One study has reported results after treatment with CD138-specific CAR T cells in five patients with relapsed/refractory myeloma. The CAR used an anti-CD138 scFv with 4-1BB costimulatory domain and lentiviral vector packaging. A mean of 0.76 × 10^7 total cells/kg were infused per patient after a variety of conditioning regimens. Cells expanded in all patients, and there were no objective responses, but stable disease lasting 3 to 6 months was seen in four patients. Low-grade CRS was seen, but—interestingly—no severe epithelial toxicities were noted.

**Other CAR Targets in Myeloma**

CAR T cells against several other cell surface antigens have demonstrated preclinical efficacy against myeloma, but clinical data are not yet available. CD38 and SLAMF7/CS1 are both logical targets given their near universal expression on plasma cells and the established clinical efficacy of monoclonal antibodies against these antigens in myeloma. However, both of these are expressed at lower levels on other hematopoietic cell types, including subsets of T cells, B cells, monocytes, natural killer cells, and hematopoietic progenitors, which raises concern about the potential for widespread immune suppression after CAR T-cell treatment. Another concern is that both CD38 and SLAMF7 are upregulated on activated T cells; thus, during in vitro expansion, the CD38-positive or SLAMF7-positive CAR T cells may be eliminated by fratricide, which potentially limits effective manufacturing. Despite these concerns, several groups have demonstrated the ability to generate CAR T cells that target CD38 and SLAMF7, and these CAR T cells do show relevant preclinical efficacy against myeloma cell lines and primary myeloma samples from patients. In addition, to overcome some of these barriers, Drent et al have used an affinity optimization approach to carefully select scFvs that bind to CD38 on myeloma cells but not on normal hematopoietic cells, which may improve the manufacturing potential and therapeutic index of this approach.

Other antigens under investigation as CAR targets in myeloma include CD44v6, Lewis Y, NKG2D ligands, CD229, and integrin beta7.

**Outstanding Questions About CAR T Cells in Myeloma**

These initial clinical studies with BCMA CAR T cells show promising activity in a group of patients with highly refractory disease, including several patients across trials with ongoing durable remissions lasting more than 1 year. However, the number of patients reported to date (< 25 per trial) remains small, and the heterogeneity among the trials with regard to patient selection, baseline prognostic risk factors, lymphodepleting conditioning, and dosing makes it difficult to draw firm conclusions about relative efficacy among CAR constructs. Larger trials of more uniformly treated patients are required to validate the safety and efficacy profiles seen so far. In addition, multiple questions remain unanswered as this approach moves forward. For example, whether a particular level of BCMA expression on myeloma cells should be required for eligibility in BCMA CAR T cell trials, and the best method to assess that expression (e.g., immunohistochemistry vs. flow cytometry) remain unknown. In addition, BCMA expression may be dynamic, and two studies have identified patients with much lower expression on residual myeloma cells after BCMA CAR T-cell therapy, which may serve a means of tumor escape. BCMA expression subsequently increases in most patients upon progression, which means that acquired mutations that confer a true antigen-negative variant, as seen with CD19 CAR T cells, are unlikely. The exact mechanism of this phenomenon is under investigation, but one possibility is increased shedding of BCMA via cleavage at the cell surface by gamma secretase or other means. Another question centers around the role of soluble BCMA and whether this
can act as a sink for the infused CAR T cells and hamper efficacy. At least so far, this does not seem to be the case; data from three trials do not demonstrate a correlation between baseline soluble BCMA concentrations and depth of response.43,45

Although lymphodepleting chemotherapy may be associated with more consistent BCMA CAR T-cell expansion,44 the optimal conditioning regimen has not yet been determined. Emerging data from CD19 CAR T-cell trials, however, suggest added benefit when fludarabine is added to cyclophosphamide, especially when more immunogenic CAR constructs are used.31,39 Thus, cyclophosphamide/fludarabine is likely to become the most commonly used regimen going forward. Also, although initial expansion of BCMA CAR T cells clearly is associated with initial response, the correlates of CAR T-cell persistence, as well as of depth and duration of response, have not yet been determined. In the BCMA CAR T-cell studies reported to date, detectable CAR T cells in the blood were seen for 3 to 6 months in most cases; some patients experienced progression shortly thereafter, and others maintained durable remissions even in the absence of detectable CAR cells.43,46 Detailed phenotypic and genotypic analyses of thepheresis product premanufacturing, the pre-infusion CAR product, the CAR T-cells postinfusion, and the bone marrow microenvironment are needed to understand the features that best correlate with and predict for sustained CAR T-cell persistence and durable remissions. This ultimately may lead to adjustments in CAR T-cell manufacturing to try to attain a final product with the most favorable biologic properties. Finally, a big unanswered question about CAR T-cell therapies in general is their cost-effectiveness and specifically whether the large price tags attached to these treatments so far ultimately will be justified by their clinical impact.

FUTURE DIRECTIONS
A number of new approaches are being explored to better optimize cellular therapies in myeloma. Upcoming studies will investigate current BCMA CAR constructs in less heavily pretreated patients, including as consolidation of upfront therapy in high-risk disease, which may allow for collection of less exhausted, more fit T cells and therefore more effective final CAR T-cell products. The design of CAR constructs continues to improve by incorporating novel costimulation,45 more efficient transduction,48 dual-antigen targeting to minimize tumor escape,86 and suicide genes that allow for rapid CAR T-cell elimination for severe toxicity.47 Combinations with immunomodulatory drugs and checkpoint inhibitors may continue to enhance CAR T-cell activity,57,88,89 and clinical trials of these combinations are underway. Finally, novel gene editing technologies, such as TALEN or CRISPR/Cas9, can be used now to generate allogeneic CAR T cells that lack major histocompatibility complex molecules and endogenous T-cell receptors to create off-the-shelf cellular therapies with less immunogenicity and lower risk of graft-versus-host disease.90,91 This technology also can reduce CAR T-cell expression of checkpoint molecules, such as PD-1, and potentially increase functionality of transferred T cells.52,93 A pilot study of this approach using gene-edited autologous NY-ESO1 TCR Tg T cells in myeloma, sarcoma, and melanoma has opened recently (NCT03399448).

CONCLUSIONS
The field of cellular therapy for myeloma continues to evolve rapidly. Gene-modified T cells, particularly BCMA CAR T cells, are showing promising response rates in early studies with patients who have highly refractory disease, and have the potential to be paradigm shifting if results are confirmed. The durability of these responses, however, has been more variable from trial to trial, so larger studies with longer follow-up times, as well as correlative analyses to understand predictors of response and relapse, are needed. Toxicities, such as cytokine release syndrome and neurotoxicity, remain challenging but are reversible in almost all patients and perhaps may be mitigated by earlier use of tocilizumab. Several additional cell therapy targets continue to be explored, including NY-ESO1, CD19, CD38, and SLAMF7, which may provide alternatives for patients whose myeloma cells are or become BCMA low or negative. Future studies may incorporate novel CAR constructs with enhanced safety and efficacy features and may treat patients earlier in their disease course.

References


Smith EL, Mailankody S, ghosh a, et al. development and evaluation of a human single chain variable fragment (scfv) derived Bcma Targeted CAR T cell vector leads to a high objective response rate in patients with advanced MM. Blood. 2017;130:742.


LUNG CANCER
Immune checkpoint inhibitors, specifically PD-1–directed agents, have changed the treatment paradigm of non–small cell lung cancer (NSCLC) and are being actively evaluated in patients with small cell lung cancer. After initial studies demonstrated survival advantage with these agents in patients with recurrent NSCLC, these agents now have demonstrated survival advantage in some patients with early-stage NSCLC. Further evaluation of these agents in combination with chemotherapy regimens and other checkpoint inhibitors is ongoing. Recent data suggest that addition of these agents to chemotherapy may improve survival compared with chemotherapy alone. Promising results have also been observed in patients with recurrent small cell lung cancer. Ongoing studies will define the role of these agents in the management of patients with small cell lung cancer. Tumor PD-L1 assessment has become standard of care since use of frontline pembrolizumab in patients with advanced NSCLC is based on tumor PD-L1 expression. Other biomarkers are being actively evaluated to identify the patients most likely to benefit from these agents. Unique adverse effects are observed with the use of immune checkpoint inhibitors. Knowledge of the adverse effects and their management is crucial in treating patients with lung cancer using immune checkpoint inhibitors.

Over the last several years, immunotherapy, specifically immune checkpoint inhibitors, has altered the treatment paradigm for several tumor types, including non–small cell lung cancer (NSCLC), and they are being actively evaluated in patients with small cell lung cancer (SCLC). In addition, there is recognition that these agents have unique adverse events (AEs), and awareness of these toxicities and their management is crucial in delivering this therapy to patients. In this review we provide an overview of the current data regarding immune checkpoint inhibitors in the management of patients with NSCLC and SCLC.

PD-1/PD-L1 INHIBITORS IN THE SECOND AND LATER LINES OF THERAPY: DATA FROM RANDOMIZED TRIALS

Nine years after the publication of the first phase I trial of the anti–PD-1 monoclonal antibody nivolumab, three anti–PD-1 or anti–PD-L1 monoclonal antibodies, nivolumab, pembrolizumab, and atezolizumab, are currently approved by the U.S. Food and Drug Administration (FDA) for therapy for advanced pretreated NSCLC. Furthermore, pembrolizumab is FDA-approved as single-agent therapy for the frontline treatment of advanced NSCLC exhibiting high expression of PD-L1 on tumor cells. All three agents have demonstrated their benefit in terms of overall survival (OS) compared with docetaxel in the second-line setting in randomized phase III trials, with OS as a primary endpoint. These trials are summarized in Tables 1 and 2. Of note, these trials were able to consistently show improvements in patients’ related outcomes and quality of life compared with docetaxel. Optimal duration of such treatments has not been formally evaluated in a well-conducted randomized trials to date and remains to be defined. CheckMate 153 (NCT02066636), an ongoing phase IIIB/IV study conducted primarily in the community setting, randomized patients still on nivolumab after 1 year of therapy to continuous treatment versus interruption, demonstrating an improvement in progression-free survival (PFS; HR 0.43; 95% CI, 0.25–0.76) in the continuously treated arm, with a trend toward improved OS as well. As a new paradigm in this very severe disease, long-term benefit of immunotherapy has also been reported, with 5-year survival of 16% with nivolumab in the phase I CA209-003 trial; 3-year OS was 26.4% in first-line patients and 19% in previously treated patients with pembrolizumab in KEYNOTE 001.

Interestingly, a recent press release announced that the phase III JAVELIN Lung 200 trial comparing anti–PD-L1 avolumab with docetaxel in second-line NSCLC did not meet its
prespecified endpoint of improving OS in patients with PD-L1 of 1% or higher (HR 0.90; 95% CI, 0.72–1.12; one-sided p = .1627). Of note, the proportion of patients in the chemotherapy arm crossing over to immune checkpoint inhibitors outside the study might have confounded this trial outcome.

THE QUEST FOR A PREDICTIVE BIOMARKER: HOW PD-1/PD-L1 INHIBITORS MOVED TO FRONTLINE THERAPY

The fact that high expression of PD-L1 enriches the patient population with responders has led to two frontline phase III randomized trials of anti–PD-1 antibodies versus standard-of-care platinum-based doublet chemotherapy. Pembrolizumab was compared with four to six cycles of one of five standard platinum-based chemotherapy regimens in the KEYNOTE 024 trial, which enrolled patients with stage IV NSCLC with a tumor proportion score of 50% or higher.9 The primary endpoint, median PFS, was increased in the pembrolizumab group (HR 0.50; 95% CI, 0.37–0.68). OS was also improved (HR 0.60; 95% CI, 0.41–0.89), as was overall response rate (ORR; 44.8% vs. 27.8%). Grade 3, 4, or 5 treatment-related AEs were less frequent in the pembrolizumab arm (26.6% vs. 53.3%). While KEYNOTE 024 established single-agent pembrolizumab in first-line therapy for advanced NSCLC with high PD-L1 expression, a second randomized trial with a similar design failed to confirm these findings. The CheckMate 026 trial randomly assigned patients with untreated stage IV or recurrent NSCLC and a PD-L1 tumor expression level of 1% or greater to receive nivolumab or up to six cycles of platinum-based chemotherapy.10 The primary endpoint, median PFS, among patients with PD-L1 expression of 5% or greater was not improved (HR 1.15; 95% CI, 0.91–1.45), nor was OS (HR 1.02; 95% CI, 0.80–1.30).10 A key difference between these two trials lies in the cutoff value of PD-L1 expression to define positivity: 50% in KEYNOTE 024, amounting to a population prevalence of approximately 30%, and 5% in CheckMate 026, amounting to a population prevalence of approximately 50%. This raises the question whether the difference in enrichment could account for discrepant results; post hoc subgroup analyses unfortunately cannot reliably answer this question in the absence of stratification for PD-L1 expression ranges.

Herein lies the controversy of PD-L1 expression as a biomarker: PD-L1 expression in pretreatment tumor specimens portends a greater likelihood of response yet is neither sufficient nor necessary, with finite albeit lower ORR in PD-L1-negative tumors. Despite this, PD-L1 expression level by immunohistochemistry on tumor cells, and to some extent on tumor-infiltrating immune cells, is currently the only predictive biomarker of immunotherapy response of clinical relevance and the only biomarker to have been prospectively validated in at least one randomized trial. Yet this biomarker suffers some serious shortcomings. Because of parallel development of the PD-1/PD-L1 inhibitors, several diagnostic antibodies (28-8, 22C3, SP142, and SP263) using various platforms (Dako, Ventana, Laica), methodologies, tumor material (archival vs. fresh), scoring methods, and PD-L1 thresholds are currently in use, with no robust overall consensus. The Blueprint PD-L1 IHC Assay Comparison Project, an industry-academy collaboration, compared the four assays used in clinical trials.10,11 Despite the observation of an identical performance of some assays on tumor cells (28-8, 22C3, SP263, and 73-10) but not SP142, it also demonstrated that interchanging the assay can lead to patient misclassification. Further comparative studies have since reached similar conclusions.12,13 These pitfalls are best highlighted when tumor samples from patients included in the phase III OAK trial were restained using the 22C3 antibody, showing markedly discrepant expression categories.14 In addition, biologic limitations of this assay must be highlighted, including temporal and treatment-related fluctuations as well as considerable intratumoral heterogeneity.15,16

Although the ultimate goal of anti–PD-1/PD-L1 inhibition is to unleash a preexisting antitumor T-cell immune response, for which PD-L1 expression can be considered a surrogate, determinants of this immune response are being investigated as predictive biomarkers. Foremost among them is tumor mutational burden (TMB), a surrogate for the presence of immunogenic neoantigens. Mutations, genetic rearrangements, insertions, and deletions have the capacity to encode tumor-specific peptides that are presented by host major histocompatibility complex molecules.17 This topic is extensively reviewed in.18,19 Specifically, frameshift insertions or deletions, in particular generate highly immunogenic tumor neoantigens,20 and consequently the overall nonsynonymous mutational load may be correlated with the probability of an underlying immune response. Accordingly, cancers with the highest median mutational burden exhibit the highest ORR to PD-1/PD-L1 inhibitors.21,22 Within distinct cancer types, a wide range of mutational burden can be observed, resulting in the fact that, from a biomarker perspective, no standard cutoff can be defined across tumors.

PRACTICAL APPLICATIONS

- PD-1–directed agents have demonstrated survival advantage in patients with recurrent NSCLC and as frontline therapy in patients with tumors that express PD-L1 at high levels.
- Initial results of trials evaluating the addition of PD-1–directed agents to chemotherapy have demonstrated survival advantage. Ongoing studies are also evaluating the combination of these agents with anti–CTLA-4 antibodies.
- PD-1–directed agents alone or in combination with anti–CTLA-4 antibodies may provide clinically meaningful benefit in patients with SCLC.
- There is a need to define biomarkers that can identify patients with lung cancer most likely to benefit from these agents.
- PD-1–directed agents may cause irAEs. Knowledge of these AEs and their management is crucial in treating patients with lung cancer with immune checkpoint inhibitors.
### TABLE 1. Phase III Trials of Anti-PD-1/PD-L1 Checkpoint Inhibitors in Advanced Pretreated NSCLC, Median OS Results

<table>
<thead>
<tr>
<th>Checkpoint Inhibitors</th>
<th>CheckMate 017 (EPAR)(^2)</th>
<th>CheckMate 057 (EPAR)(^3)</th>
<th>OAK (ESMO 2016, WCLC 2016)(^8)</th>
<th>KEYNOTE 010 (EPAR, WCLC 2016, ASCO 2017)(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study drug</strong></td>
<td>Nivo 3 mg/kg q2w</td>
<td>Nivo 3 mg/kg q2w</td>
<td>Atezo 1,200 mg q3w</td>
<td>Pembro 2 mg/kg q3w, pembro 10 mg/kg q3w</td>
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<tr>
<td><strong>No. of patients</strong></td>
<td>272</td>
<td>582</td>
<td>850</td>
<td>1,033</td>
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<tr>
<td><strong>Patient population</strong></td>
<td>2L SQ stage IIIB/IV NSCLC</td>
<td>2L+ NSQ stage IIIB/IV NSCLC</td>
<td>2L+ stage IIIB/IV or recurrent NSCLC</td>
<td>2L+ metastatic NSCLC (PD-L1 TPS ≥ 1%)</td>
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<tr>
<td><strong>Primary endpoint</strong></td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
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<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Nivo</td>
<td>135 patients</td>
<td>292 patients</td>
<td>425 patients</td>
<td>344 patients</td>
</tr>
<tr>
<td>Doc</td>
<td>137 patients</td>
<td>290 patients</td>
<td>425 patients</td>
<td>346 patients</td>
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<tr>
<td><strong>Median OS, months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross histology</td>
<td>13.8</td>
<td>6.9</td>
<td>8.9</td>
<td>7.6</td>
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<tr>
<td>Squamous</td>
<td>9.23</td>
<td>6.01</td>
<td>HR 0.59 (96.85% CI, 0.43–0.81)</td>
<td>HR 0.73 (95% CI, 0.54–0.89)</td>
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<tr>
<td>Nonsquamous</td>
<td>12.19</td>
<td>9.36</td>
<td>HR 0.73 (95.92% CI, 0.59–0.89)</td>
<td>HR 0.73 (95% CI, 0.60–0.89)</td>
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<tr>
<td><strong>&lt; 1% (TC0 and TC0)(^a)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Cross histology</td>
<td>12.6</td>
<td>8.9</td>
<td>HR 0.75 (95% CI, 0.59–0.96)</td>
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<tr>
<td>Squamous</td>
<td>8.7(^a)</td>
<td>5.9(^a)</td>
<td>HR 0.58 (95% CI, 0.37–0.92)</td>
<td>HR 0.82(^c)</td>
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<td>Nonsquamous</td>
<td>10.4(^a)</td>
<td>10.1(^a)</td>
<td>HR 0.90 (95% CI, 0.66–1.24)</td>
<td>HR 0.75(^c)</td>
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<td><strong>≥ 1% (TC1/2/3 or IC1/2/3)(^a)</strong></td>
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<tr>
<td>Cross histology</td>
<td>15.7</td>
<td>10.3</td>
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<td>10.5(^c)</td>
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<td>13.4(^c)</td>
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<th>Checkpoint Inhibitors</th>
<th>CheckMate 017 (EPAR)</th>
<th>CheckMate 057 (EPAR)</th>
<th>OAK (ESMO 2016, WCLC 2016)</th>
<th>KEYNOTE 010 (EPAR, WCLC 2016, ASCO 2017)</th>
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<tr>
<td>Squamous</td>
<td>9.3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.2&lt;sup&gt;b&lt;/sup&gt;</td>
<td>9.9&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.71&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>9.0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>17.6</td>
<td>0.72&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>HR 0.59 (95% CI, 0.43–0.82)</td>
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<td>11.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>≥ 5% (TC2/3 or IC2/3)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>16.3</td>
<td>0.67 (95% CI, 0.49–0.90)</td>
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<td></td>
<td>HR 0.43</td>
<td></td>
<td>11.3&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>≥ 10% (NA)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>16.3</td>
<td>0.67 (95% CI, 0.49–0.90)</td>
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<tr>
<td>Cross histology</td>
<td></td>
<td></td>
<td>10.8</td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>7.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>14.9</td>
<td>0.54 (95% CI, 0.38–0.77)</td>
</tr>
<tr>
<td></td>
<td>HR 0.50 (95% CI, 0.28–0.89)</td>
<td></td>
<td>17.3</td>
<td></td>
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<tr>
<td>Nonsquamous</td>
<td>19.4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 mg/kg, HR 0.54 (95% CI, 0.38–0.77)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>10 mg/kg, HR 0.50 (95% CI, 0.36–0.70)&lt;sup&gt;f&lt;/sup&gt;</td>
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<tr>
<td>≥ 50% (TC3 or IC3)&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>22.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>Cross histology</td>
<td></td>
<td></td>
<td>8.7&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Squamous</td>
<td>17.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>11.6&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.5&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
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<tr>
<td></td>
<td>HR 0.32 (95% CI, 0.20–0.53)</td>
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<tr>
<td>Nonsquamous</td>
<td></td>
<td>22.5&lt;sup&gt;c&lt;/sup&gt;</td>
<td>8.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.35&lt;sup&gt;e&lt;/sup&gt;</td>
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</tbody>
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<sup>a</sup>Bristol-Myers Squibb PD-L1 assay measures PD-L1 expression on tumor cells; Roche PD-L1 assay measures PD-L1 expression on tumor and immune cells.

<sup>b</sup>ASCO 2015.

<sup>c</sup>WCLC 2016.
<table>
<thead>
<tr>
<th>Study drug</th>
<th>CheckNate 017 (EPAR)²</th>
<th>CheckMate 057 (EPAR)³</th>
<th>OAK (ESMO 2016, WCLC 2016)⁴</th>
<th>KEYNOTE 010 (EPAR, WCLC 2016, ASCO 2017)⁷</th>
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<tbody>
<tr>
<td></td>
<td>Nivo 3 mg/kg q2w</td>
<td>Nivo 3 mg/kg q2w</td>
<td>Atezo 1,200 mg q3w</td>
<td>Pembro 2 mg/kg q3w, pembro 10 mg/kg q3w</td>
</tr>
<tr>
<td>No. of patients</td>
<td>272</td>
<td>582</td>
<td>850</td>
<td>1,033</td>
</tr>
<tr>
<td>Patient population</td>
<td>2L SQ stage IIIB/IV NSCLC</td>
<td>2L+ NSQ stage IIIB/IV NSCLC</td>
<td>2L+ stage IIIB/IV or recurrent NSCLC</td>
<td>2L+ metastatic NSCLC (PD-L1 TPS ≥ 1%)</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
<td>OS</td>
</tr>
<tr>
<td>Study drug</td>
<td>Nivo</td>
<td>Doc</td>
<td>Nivo</td>
<td>Doc</td>
</tr>
<tr>
<td>No. of patients</td>
<td>135 patients</td>
<td>137 patients</td>
<td>292 patients</td>
<td>290 patients</td>
</tr>
<tr>
<td>1-year OS, %</td>
<td>42.1</td>
<td>23.7</td>
<td>50.5</td>
<td>39.0</td>
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<tr>
<td>18-months OS, %</td>
<td>28b</td>
<td>13b</td>
<td>39c</td>
<td>23c</td>
</tr>
<tr>
<td>2-year OS, %</td>
<td>23d</td>
<td>8d</td>
<td>29d</td>
<td>16d</td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>3.48</td>
<td>2.83</td>
<td>2.33</td>
<td>4.21</td>
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<tr>
<td></td>
<td>(95% CI, 0.47–0.81)</td>
<td>(95% CI, 0.77–1.11)</td>
<td>HR 0.92 (95% CI, 0.82–1.10)</td>
<td>HR 0.95 (95% CI, 0.73–1.04)</td>
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<tr>
<td>ORR, %</td>
<td>20</td>
<td>9</td>
<td>19</td>
<td>12</td>
</tr>
<tr>
<td>mDOR, months</td>
<td>25.2</td>
<td>8.4</td>
<td>18.3</td>
<td>5.6</td>
</tr>
<tr>
<td>Safety</td>
<td>TRAEs, %</td>
<td>58b</td>
<td>69b</td>
<td>88b</td>
</tr>
<tr>
<td>Grade 3–5 TRAEs%</td>
<td>7b</td>
<td>57b</td>
<td>10b</td>
<td>54b</td>
</tr>
</tbody>
</table>

²WCLC 2015.
³ASCO 2015.
⁴ESMO 2015.
⁵ESMO 2016.
⁶Grade 3–5 TRAEs.
types. Despite these caveats, it has now been demonstrated retrospectively that TMB derived from whole-exome sequencing identifies a subgroup benefitting from frontline nivolumab compared with chemotherapy. Furthermore, the total-exome mutation rate correlated well with the rate derived from an in silico analysis filtering on a panel of 315 genes in the FoundationOne comprehensive genomic profile, and correlation was shown between tow analysis in a subset of samples. Of note, clonality of the neoantigen seems instrumental in achieving durable benefit from PD-1/PD-L1 inhibition, while subclonal neoantigens are enriched in poor responders. Tumors with preexisting immunity, represented by abundance of tumor-infiltrating cells, dense functional CD8+ T-cell infiltration reflected by increased interferon-gamma signaling, expression of checkpoint markers including PD-L1, and high mutational burden, so-called inflamed tumors, are likely to respond to single-agent anti–PD-1/PD-L1 inhibitors; conversely, tumors with the excluded infiltrate or stromal T-cell phenotype (T cells are unable to infiltrate the tumor), as well as immunologically ignorant tumors that contain very low infiltration of T cells, are mostly resistant.

Other immune biomarkers are under active investigation, including immune gene signatures, gut microbiome characteristics, and host HLA characteristics. These independent factors will probably need to be prioritized and possibly assembled in an immunotherapy-dedicated predictive signature in the future but with potential need for adjustments with the emergence of new immunotherapy combinations under investigations.

**IMPROVING FRONTLINE STRATEGY**

On the basis of preclinical evidence suggesting that the antitumor activity of chemotherapy is also mediated through immunologic effects, including a reduction of T-regulatory cell activity and immunogenic cell death with enhanced tumor-antigen presentation, many trials are exploring combinations of immune checkpoint blockade with chemotherapy. A randomized phase II trial demonstrated that the addition of pembrolizumab to standard-of-care carboplatin and pemetrexed in patients with advanced nonsquamous NSCLC yielded a significantly superior response rate (primary endpoint 55% vs. 29%) compared with chemotherapy alone and a shorter time to response (1.5 vs. 2.7 months). Updated results showed an improvement in median PFS (19.0 vs. 8.9 months; HR for progression or death, 0.54), as well as an improvement in median OS (not reached vs. 20.9 months; HR for death, 0.59). A phase III trial (KEYNOTE 189) with similar design has completed accrual, and recently it was announced that the dual primary endpoints of OS and PFS were met, on the basis of an interim analysis conducted by the independent data monitoring committee.

**Overall Survival and Progression-Free Survival**

In this trial, subgroup analysis by PD-L1 expression, in particular in the group with less than 50% of PD-L1, and TMB will be of paramount importance.

Recently, first results of the phase III IMpower150 study showed that atezolizumab and bevacizumab plus paclitaxel/carboplatin significantly improved PFS (median PFS 8.3 vs. 6.8 months; HR 0.62; p < .0001) compared with chemotherapy/bevacizumab. Of note, there is a strong scientific rationale to support this four-drug combination, notably a very well described role of VEGF in the immunotolerance mechanisms, affecting T-cell trafficking, antigen presentation, proliferation of regulatory T cells, and accumulation of myeloid-derived suppressor cells. PFS benefit was seen regardless of PD-L1 immunohistochemistry status, including PD-L1-negative patients (TC0/IC0; HR 0.77). On the basis of the whole intention-to-treat population, IMpower150 is the first immunotherapy trial significantly beneficial in patients with alterations in EGFR and ALK (n = 108; HR 0.59). An immune gene signature, the T-eff signature (defined by messenger RNA expression of three genes (PDL1, CXCL9, and IFNG) was shown to offer similar predictive ability to PD-L1 expression, with a benefit of the strategy across all related categories as well.

Comparison of atezolizumab/chemotherapy with bevacizumab/chemotherapy, as well as OS and maturation of subgroups outcomes, is awaited for this trial.

Also recently, the phase III CheckMate 227 study met its coprimary endpoint of PFS with nivolumab/ipilimumab combination versus chemotherapy in patients with first-line advanced NSCLC whose tumors have high (≥ 10 mutations/megabase) TMB regardless of PD-L1 expression. In the study, TMB was evaluated using Foundation Medicine’s analytically validated panel. Data may be presented before the next ASCO Annual Meeting for CheckMate 227 and KEYNOTE 189.

On the other hand, AstraZeneca had previously announced in 2017 that the combination of durvalumab and tremelimumab did not meet the primary endpoint of improving PFS compared with standard of care in patients whose tumors express PD-L1 on 25% or more of their cancer cells in the phase III MYSTIC trial. As a secondary endpoint, although not formally tested, durvalumab monotherapy had not met a prespecified threshold of PFS benefit over standard of care either. The trial continues to assess coprimary endpoints of OS, and results are expected in 2018.

For the vast majority of patients, answers to these open questions will be key in supporting a rational immunotherapeutic approach. Next trials will have to contribute to define better predictive tumor biomarkers, refined patient selection, optimal personalized multimodal combinations, resistance mechanisms, and adequate duration, intervals, and dosage of anticancer immunotherapy drugs.

**IMMUNE CHECKPOINT INHIBITORS IN PATIENTS WITH SCLC**

Systemic therapy for SCLC is associated with a generally poor prognosis, with median OS of approximately 10 months for patients with SCLC who present with extensive stage of the disease. Attempts to extend the benefit of chemotherapy with consolidative thoracic radiation showed some incremental benefit, but only 10% of patients are alive at 2 years. Patients with limited-stage SCLC appear to do
somewhat better, with median OS of approximately 2 years with current standard treatment of chemoradiation.\textsuperscript{42–44} The benefit of systemic therapy in the relapsed disease setting is quite limited and indeed negligible in patients with platinum-refractory disease.\textsuperscript{45–47} Similar to the experience with other solid malignancies, immune checkpoint inhibitors are being actively evaluated in SCLC, and early results are encouraging.

**IMMUNOTHERAPY TARGETING CTLA-4**

Ipilimumab, an anti–CTLA-4 monoclonal antibody, was studied in SCLC in combination with chemotherapy. Treatment-naïve patients with end-stage SCLC were randomized to doublet chemotherapy (carboplatin/paclitaxel) alone or in combination with ipilimumab. There was a modest signal of improved efficacy with the phased sequential combination regimen: immune-related PFS was 5.7 versus 6.4 versus 5.3 months (HR 0.64; p = .03) for the phased combination compared with control (Table 1).\textsuperscript{48} A confirmatory phase III evaluation of phased combination ipilimumab along with platinum/etoposide followed by maintenance ipilimumab failed to improve OS over chemotherapy alone; median OS was 11 versus 10.9 months (HR 0.94; 95% CI, 0.81–1.09).\textsuperscript{49} In addition, there was also no significant improvement in median PFS (4.6 vs. 4.4 months; HR 0.85; 95% CI, 0.75–0.97), and ORR was identical at 62% in each arm. Immune-related toxicity, including diarrhea, rash, and colitis, resulted in higher rates of treatment discontinuation (18% vs. 2%) and death (5% vs. 2%). Because of the negative result of this confirmatory phase III, there is currently no role for the use of ipilimumab plus chemotherapy in the management of patients with SCLC. However, other strategies of chemoimmunotherapy combination targeting PD-1 are under evaluation and may result in positive outcomes.

**PD-1–TARGETED IMMUNOTHERAPY**

**Treatment-Naïve SCLC**

There are no mature clinical trial data for PD-1–targeted agents in the frontline management of SCLC, but studies are currently under way in previously untreated patients with both limited-stage and extensive-stage SCLC trials (Table 1). The KEYNOTE 604 and REACTION clinical trials are currently evaluating the combination of pembrolizumab along with platinum/etoposide in patients with treatment-naïve extensive-stage SCLC. Similarly, atezolizumab is being studied in combination with platinum/etoposide, while the regimen of durvalumab, tremelimumab, and platinum doublet chemotherapy is being compared against platinum doublet alone.

**Maintenance Immunotherapy**

Although maintenance therapy is not a standard treatment approach for SCLC, temsirolimus and sunitinib both showed signal of benefit in small phase II studies.\textsuperscript{50} Immune checkpoint inhibitors are now being tested in this setting. Pembrolizumab failed to show any signal of efficacy in a multicenter phase II trial that enrolled 45 patients; median PFS was 1.4 months (95% CI, 1.3–4 months) and median OS was 9.4 months (95% CI, 6.1–15.2) and 30% at 1 year.\textsuperscript{51} Subset analysis suggested possible benefit in patient with PDL1-positive tumors (5.5 vs. 1.3 months). A more definitive evaluation of maintenance nivolumab alone or in combination with ipilimumab is ongoing both in limited-stage SCLC (STIMULI trial) and extensive-stage SCLC (CheckMate 451 trial).

**Relapsed SCLC**

The strategy of targeting the PD-1 pathway alone or along with anti–CTLA-4 agents has shown promising results in patients with relapsed SCLC. The phase I/II CheckMate 032 trial (Table 1) explored the efficacy of nivolumab alone or in combination with ipilimumab in patients who progressed following prior systemic chemotherapy.\textsuperscript{52} The ORR was 10% with nivolumab alone and between 19% and 33% for the combination depending on the different schedules and doses of ipilimumab. One-year OS was 33% for nivolumab and up to 43% with the combination. Higher doses of ipilimumab were associated with increased frequency of grade 3 or 4 AEs, at 30% versus 13%. Updated results of the CheckMate 032 study with approximately 400 patients confirmed the increased ORR with the combination at 22% versus 9%.\textsuperscript{53} On the basis of the overall benefit demonstrated in the study, both single-agent nivolumab and the combination have been endorsed by professional bodies and included in management guidelines for oncologists. The results of the CheckMate 331 study, which compared topotecan or amrubicin with nivolumab as second-line treatment of SCLC, are awaited as a confirmatory study of this initial result from the CheckMate 032 study. The KEYNOTE 028 study investigated the clinical efficacy of pembrolizumab in 24 patients with relapsed SCLC whose tumors showed 1% or higher PD-L1 staining. The ORR was 33%, with a median response duration of 19.4 months and a 1-year OS rate of 37.7%.\textsuperscript{54} Another approach to incorporate immunotherapy into SCLC management is through combination with radiation. Radiation has been shown to be immunogenic and can theoretically prime cancer cells for immunotherapy. Radiation causes cellular apoptosis and exposes the immune system to additional antigens.\textsuperscript{55} Major histocompatibility complex I protein, which is poorly expressed in SCLC, can be induced along with other neoantigens following ionizing radiation treatment.\textsuperscript{56,57} Ongoing studies of immunotherapy in combination with radiation in various settings as well as other immunotherapy studies in previously treated patients with end-stage SCLC are detailed in Table 1.

**PREDICTIVE BIOMARKERS**

Available results of immunotherapy studies in SCLC showed benefit in only a limited subset of patients. It is therefore important to establish a reliable predictive biomarker to better select patients who are most likely to benefit. The expression of PD-L1 is generally low in SCLC and has not shown a strong association with clinical efficacy, unlike in NSCLC, in which high PD-L1 expression correlates with higher ORR and longer duration of benefit.\textsuperscript{2,15,56,59} A post hoc analysis correlating PD-L1 status and clinical outcome in the CheckMate
032 study showed poor correlation of clinical benefit with PDL1 expression.52 However, TMB appeared very promising and is strongly associated with benefit of both single-agent nivolumab and the combination of nivolumab and ipilimumab.60 Prospective validation of TMB as a predictive biomarker in SCLC will help optimize the use of immunotherapy and potentially define a new subset of patients.

CONCLUSION
There is a positive and encouraging signal of efficacy of immunotherapy in SCLC. In particular, agents targeting the PD-1 pathway have shown reproducible efficacy in relapsed SCLC. Results of prospective confirmatory studies are now awaited to guide regulatory approval (Table 3). Other strategies such as chemoimmunotherapy in the frontline and maintenance immunotherapy following definitive chemoradiation are under active investigation and likely to change the treatment paradigm for this disease.

TOXICITIES OF CHECKPOINT INHIBITORS
There is a recognition that immune checkpoint inhibitors have unique AEs, and awareness of these toxicities and their management is crucial in delivering this therapy to patients.61 Though the precise etiology of each immune-related AE (irAE) is not known, these AEs result from immune system–induced tissue damage in the affected organ. This tissue damage involves T cells in many instances, but certain toxicities may result from activation of the humoral immunity as well release of cytokines.52,63 Because these toxicities occur only in a subset of patients, there is speculation that host factors such as genetic variability may determine the occurrence of these toxicities. However, at least in one study, no connection between genetic markers and risk of irAEs was found.64 More studies are needed to define factors that may predict for irAEs. It is possible that the factors influencing the development of different toxicities may vary.

In general, irAEs are more commonly observed with anti–CTLA-4 agents than PD-1–directed agents, possibly because the former affects an early step of immune activation, whereas PD-1–directed agents are active much more in the peripheral tissues. However, the organs affected can vary with anti–CTLA-4 and anti–PD-1. Colitis and hypophysitis are more common with anti–CTLA-4 drugs, whereas hypothyroidism is more common with PD-1–directed agents.

ONSET OF IRAES
irAEs tend to occur within 3 months of starting therapy, though late toxicities are well recognized, including toxicities occurring after cessation of checkpoint inhibitors.65 Certain toxicities tend to occur earlier, such as skin and liver toxicities, whereas gastrointestinal toxicities and endocrinopathies tend to occur after the initial weeks of therapy. It is extremely uncommon to observe pneumonitis with PD-1–directed agents beyond the first 3 to 6 months. The knowledge of timelines of these irAEs may guide in evaluating new symptoms in patients on immune checkpoint inhibitors.

The incidence of irAEs is higher with the combination of PD-1–directed agents and anti–CTLA-4 antibodies, and the onset of these toxicities can be earlier compared with the onset of the same toxicities with single-agent PD-1–directed drugs.

COMMON TOXICITIES
PD-1–Directed Agents
In each of the randomized trials of PD-1–directed agents in patients with NSCLC, AEs were less frequent with these agents compared with AEs observed with chemotherapy.2,4 The median duration of therapy in these studies ranged from 5 to 10 cycles, and approximately 5% to 8% of patients discontinued therapy because of AEs.

Fatigue was the most common AE, followed by nausea, in patients treated with these agents (Table 4). The causality of these two AEs in most patients is unclear. Hypothyroidism was the most common irAE observed in these studies, occurring in approximately 8% of patients. Some of the other irAEs observed in these trials were hyperthyroidism, hepatitis, adrenal insufficiency, myositis, myocarditis, and type 1 diabetes. The incidence of these irAEs was generally less than 3%. Pneumonitis has been observed with each of the PD-1–directed agents in 1% to 5% of patients, with grade 3 or higher pneumonitis occurring in about 1% of the patients.

Toxicities of Combination Regimens
Several studies have evaluated PD-1–directed agents in combination with chemotherapy drugs and other immunotherapy drugs, primarily anti–CTLA-4 drugs.34,35,66

The KEYNOTE 21 trial evaluated the addition of pembrolizumab to several different chemotherapy regimens and found that it was safe to add pembrolizumab at full dose with standard doses of chemotherapy drugs. KEYNOTE 21G randomized patients with nonsquamous NSCLC to carboplatin and pemetrexed with or without pembrolizumab.34 The median duration of therapy in patients who received pembrolizumab with chemotherapy was 8 months, and it was 4.9 months in patients who received chemotherapy alone. The AE-related treatment discontinuation rate was similar in the two groups of patients. In this trial, fatigue, nausea, diarrhea, rash, and alopecia occurred at least 10% more often in patients who received pembrolizumab in combination with chemotherapy. The incidence of grade 3 and 4 toxicities was not much different with the addition of pembrolizumab.

Other studies that have evaluated the addition of PD-1–directed agents with chemotherapy have not found any different toxicities than what is expected with these agents when administered independently.66
### TABLE 3. Immunotherapy Trials in ES-SCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Phase of Trial</th>
<th>No. of Patients</th>
<th>PFS (Months)</th>
<th>OS (Months)</th>
</tr>
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<tbody>
<tr>
<td><strong>Treatment-naive SCLC</strong></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>Ipilimumab + carboplatin/paclitaxel vs. ipilimumab + carboplatin/paclitaxel (cycle 3) vs. carboplatin/paclitaxel</td>
<td>II</td>
<td>130</td>
<td>5.7 vs. 6.4 vs. 5.3 (HR 0.75, 0.64)*</td>
<td>9.1 vs. 12.5 vs. 10.5 (HR 0.89, 0.76)</td>
</tr>
<tr>
<td></td>
<td>Ipilimumab + platinum/VP16 (cycle 3) vs. placebo + platinum/VP16</td>
<td>III</td>
<td>1,132</td>
<td>4.6 vs. 4.4 (HR 0.85)</td>
<td>11 vs. 10.9 (HR 0.94)</td>
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<tr>
<td></td>
<td>NCT02402920: Platinum/etoposide + radiation ± pembrolizumab</td>
<td>II</td>
<td>I</td>
<td>Ongoing</td>
<td></td>
</tr>
<tr>
<td><strong>Extensive-stage SCLC</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>REACTION</td>
<td>Platinum/etoposide ± pembrolizumab</td>
<td>II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
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<tr>
<td>KEYNOTE-604</td>
<td>Platinum/etoposide ± pembrolizumab</td>
<td>III</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
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<tr>
<td>IMpower133</td>
<td>Carboplatin/etoposide ± atezolizumab</td>
<td>III</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
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<tr>
<td>Caspian</td>
<td>Platinum/etoposide + durvalumab ± tremelimumab vs. Chemotherapy alone</td>
<td>III</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
</tr>
<tr>
<td>MCC-18914</td>
<td>Platinum/etoposide followed by thoracic radiation ± Nivolumab + ipilimumab</td>
<td>I/II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT02402920</td>
<td>Platinum/etoposide followed by thoracic radiation ± pembrolizumab</td>
<td>I</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Pembrolizumab</td>
<td>II</td>
<td>45</td>
<td>4.7*</td>
<td>9.4</td>
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<tr>
<td>CheckMate 451</td>
<td>Nivolumab, nivolumab + ipilimumab, placebo</td>
<td>III</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td><strong>Relapsed SCLC</strong></td>
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<tr>
<td>I/II</td>
<td>Nivolumab vs. Nivolumab 1 mg/kg, ipilimumab 3 mg/kg vs. Nivolumab 3 mg/kg, ipilimumab 1 mg/kg</td>
<td>I/II</td>
<td>216</td>
<td>1.4 vs. 2.6 vs. 1.4</td>
<td>4.4 vs. 7.7 vs. 6</td>
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<tr>
<td>IB</td>
<td>Pembrolizumab</td>
<td>II</td>
<td>20</td>
<td>1.9</td>
<td>9.7</td>
</tr>
<tr>
<td>AFT17</td>
<td>Pembrolizumab vs. topotecan</td>
<td>II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
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<tr>
<td>CheckMate 331</td>
<td>Nivolumab vs. topotecan or amrubicin</td>
<td>III</td>
<td>–</td>
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<td>Ongoing</td>
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<tr>
<td>IFCT-1603</td>
<td>Atezolizumab vs. topotecan or carboplatin/etoposide</td>
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<td>–</td>
<td>Ongoing</td>
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<td>MISP-MK3475</td>
<td>Pembrolizumab + paclitaxel</td>
<td>II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
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<tr>
<td>PembroPlus</td>
<td>Pembrolizumab + irinotecan</td>
<td>I/II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
</tr>
<tr>
<td>CA001-030</td>
<td>BMS-986012 ± nivolumab</td>
<td>I/II</td>
<td>–</td>
<td>–</td>
<td>Ongoing</td>
</tr>
<tr>
<td>KEYNOTE-158</td>
<td>Pembrolizumab</td>
<td>II</td>
<td>II</td>
<td>Ongoing</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 3. Immunotherapy Trials in ES-SCLC (Cont'd)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Arms</th>
<th>Phase of Trial</th>
<th>No. of Patients</th>
<th>PFS (Months)</th>
<th>OS (Months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02937818</td>
<td>Durvalumab + tremelimumab vs. AZD1775 + carboplatin</td>
<td>II</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winship 3112-15</td>
<td>Tremelimumab + durvalumab ± radiation</td>
<td>II</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M16-300</td>
<td>Nivolumab + rovalpituzumab ± ipilimumab</td>
<td>I</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AAAQ8257</td>
<td>SGI-110 followed by durvalumab + tremelimumab</td>
<td>I</td>
<td>Ongoing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ES, end-stage; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer; VP16, etoposide.
TABLE 4. Adverse Events With PD-1–Directed Agents in Patients With NSCLC

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Any Grade (%)</th>
<th>Grades 3 and 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16–20</td>
<td>1</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10–14</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Rash</td>
<td>9–13</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>2–5</td>
<td>2</td>
</tr>
</tbody>
</table>

Summary of adverse events from CheckMate 057,7 KEYNOTE-10,3 and OAK.4
Abbreviations: NSCLC, non–small cell lung cancer.

4 weeks combined with tremelimumab at 1 mg/kg every 4 weeks, with discontinuation of tremelimumab after four cycles, was found to have an acceptable toxicity profile and demonstrated clinical activity. The most common toxicities observed among the 18 patients treated in this cohort were pruritus, skin rash, diarrhea, hypothyroidism, and elevated liver enzymes. Three patients (17%) discontinued therapy because of AEs.

CheckMate 12 evaluated the combination of nivolumab and ipilimumab as frontline therapy for patients with advanced NSCLC.68 Several schedules of administering both agents every 3 weeks were evaluated but found not to be tolerable because of high rates of grade 3 and 4 AEs. The schedules identified as tolerable and suitable for further development in patients with NSCLC were nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg given every 6 or 4 weeks combined with tremelimumab 1 mg/kg every 6 or 4 weeks. Skin toxicity, gastrointestinal toxicities and endocrine abnormalities were the common AEs. The incidence of these toxicities was higher with the combination than what is expected with single-agent nivolumab. Five patients (13%) in the ipilimumab every 6 weeks cohort and four patients (10%) in the ipilimumab every 12 weeks cohort discontinued therapy because of AEs.

Finally, in CheckMate 032, patients with recurrent SCLC were randomized to nivolumab alone or combined with ipilimumab.55 In this study, treatment-related AEs occurred in 73% of the patients treated with the combination compared with 55% in patients treated with nivolumab. Treatment discontinuation due to AEs occurred in 13% and 3%, respectively. Also skin, gastrointestinal, hepatic, and endocrine-related toxicities were more common in patients who received the combination. There were four treatment-related deaths (myasthenia gravis, encephalitis, pneumonitis, and hepatitis) among the patients who received the combination compared with one pneumonitis-related death among patients treated with nivolumab alone.

GENERAL PRINCIPLES OF MANAGEMENT

Several recent guidelines have addressed management of individual irAEs observed with PD-1–directed agents.65,69 Broad guidelines for management of irAEs are listed in Table 5.

TABLE 5. Principles of Management of Immune-Related AEs With PD-1–Directed Agents

<table>
<thead>
<tr>
<th>Grade of Toxicity* (Severity)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (mild)</td>
<td>Symptomatic management. Can continue therapy. Immune suppression not needed.</td>
</tr>
<tr>
<td>2 (mild to moderate)</td>
<td>Symptomatic management. Consideration for discontinuation of therapy until toxicity resolves to grade 1. Consider immune suppression if toxicity intolerable or persistent.</td>
</tr>
</tbody>
</table>

*CTC criteria version 4.03.
Abbreviation: AE, adverse event.

Certain steps should be considered when managing patients treated with these agents:

1. A detailed history (including history of autoimmune diseases), physical examination, and laboratory tests (including thyroid tests) should be performed.
2. Patients should be educated about the toxicities (“Call if you notice any increase in frequency or change in consistency of your bowel movements”).
3. Assessments should be conducted at least once a cycle for the first 3 months, including physical examination and laboratory tests. Thyroid function tests should be repeated every cycle for the first 3 months and then at least every two or three cycles.
4. Physicians and trainees, who may also manage your patients, should be educated about irAEs.
5. If irAE is a concern, the threshold to start steroids or other immunosuppressants should be low.
6. Immune suppression should be tapered gradually after resolution of irAEs.
7. Consultants should be involved early and promptly.
8. Long-term effects of immunosuppressants (e.g., Pneumocystis pneumonia prophylaxis) should be addressed.

Restarting PD-1–directed agents in patients who have experienced irAEs can be challenging. The toxicity generally must resolve to grade 1 before consideration for restarting can be made. Usually these drugs are not restarted if a patient experiences grade 3 or 4 toxicity. There may not be a need to restart the drug if the patient’s cancer is well controlled.

USE OF CHECKPOINT INHIBITORS IN SPECIAL POPULATIONS

Most clinical trials excluded patients with histories of autoimmune disorders. Several factors must be considered before making a decision to use immune checkpoint inhibitors in these patients. These include severity of the autoimmune disorder, need for immune suppression, and status of the
cancer. Case reports and retrospective analyses suggest that these patients could be treated with checkpoint inhibitors. Although these patients may experience worsening of their autoimmune disorders, in most patients this can be managed safely. It is very important to engage other consultants involved in the management of a patient’s autoimmune disorder if immune checkpoint inhibitors are being considered.

Another group of patients not included in clinical trials of checkpoint inhibitors are those with histories of organ transplantation. Because graft rejection has been reported with the use of these agents, the general recommendation is to avoid these agents in these patients. If these agents are considered, judicious decision making is warranted, and inclusion of patient’s transplantation physicians in the decision making process is very crucial.

### IRAES AND TUMOR RESPONSE

Data regarding the development of irAEs and patient outcomes are mixed. In a retrospective analysis of 90 patients with NSCLC by Owen et al, survival was longer in patients who developed irAEs (13 vs. 5.8 months). In a separate analysis of 134 patients with NSCLC, survival was also longer in patients who developed irAEs. In a study of patients with melanoma treated with ipilimumab, there was no difference in outcomes among patients who did or did not develop irAEs. It is possible that certain irAEs and not all irAEs correlate with outcomes. Studies have shown that patients with melanoma who develop vitiligo have higher response with PD-1–directed agents.

### SUMMARY OF IRAES

Randomized phase III trials have shown that toxicities with PD-1–directed agents are less than with docetaxel in patients with recurrent NSCLC. irAEs are not common, with the most common events being hypothyroidism, hyperthyroidism, skin rash, pneumonitis, and hepatitis. PD-1–directed agents can be combined safely with platinum-based combination chemotherapy. No additional toxicities were observed. However, combinations of PD-1–directed agents and anti–CTLA-4 agents required modification of the dose and schedule to limit AEs. Institution of immune-suppressive therapy to manage irAEs should be prompt and should not be withheld out of concern for limiting efficacy of the checkpoint inhibitors.

### References


“My Patient Was Diagnosed With Nontargetable Advanced Non–Small Cell Lung Cancer. What Now?” Diagnosis and Initial Treatment Options for Newly Diagnosed Patients With Advanced NSCLC

Melissa Johnson, MD, Nathan A. Pennell, MD, PhD, and Hossein Borghaei, MS, DO

OVERVIEW

Although lung cancer remains the leading cause of cancer-related mortality in the United States and worldwide, the rate at which Americans are dying from lung cancer continues a decline that started in the 1990s. The primary reasons behind this improvement are reduced rates of tobacco use and the early impact of screening as well as a growing understanding of the underlying biology of non–small cell lung cancer (NSCLC) as well as recent successes of novel therapeutic strategies more effective and tolerable than platinum-based chemotherapy. We now recognize distinct subtypes of NSCLC, defined by molecular profiling and immunohistochemistry, with different treatment algorithms, including targeted small molecular inhibitors and immunotherapy for each. Both biomarker selection and preferred frontline strategies continue to evolve rapidly, making it difficult for many practitioners to keep up. In this review, we will first describe the recommended initial workup for a patient with advanced or metastatic NSCLC in 2018; next, we present an algorithm to aid oncologists in the selection of the most appropriate therapy for treatment-naive patients with NSCLC, and finally, we offer a look into future treatment options through a discussion of ongoing clinical trials.

Although lung cancer remains the leading cause of cancer-related mortality in the United States and worldwide, the rate at which Americans are dying from lung cancer continues a decline that started in the 1990s. Improving survival can be explained, in large part, by a growing understanding of the heterogeneous biology of non–small cell lung cancer (NSCLC) as well as recent successes of novel therapeutic strategies more effective and tolerable than platinum-based chemotherapy. We now recognize distinct subtypes of NSCLC, defined by molecular profiling and immunohistochemistry, with different treatment algorithms, including targeted small molecular inhibitors and immunotherapy for each. Both biomarker selection and preferred frontline strategies continue to evolve rapidly, making it difficult for many practitioners to keep up. In this review, we will first describe the recommended initial workup for a patient with advanced or metastatic NSCLC in 2018; next, we present an algorithm to aid oncologists in the selection of the most appropriate therapy for treatment-naive patients with NSCLC, and finally, we offer a look into future treatment options through a discussion of ongoing clinical trials.

DIAGNOSTIC APPROACH FOR PATIENTS WITH SUSPECTED LUNG CANCER

Staging Studies

As the treatment algorithm for patients with advanced NSCLC becomes more complex, ensuring a comprehensive initial workup is increasingly important to ensure that newly diagnosed patients are receiving the most appropriate life-extending therapies (Table 1). The American College of Chest Physicians revised guidelines in 2013 on routine workup and diagnosis of patients with suspected or confirmed lung cancer.

All patients with a pathologic diagnosis of NSCLC require a basic set of imaging studies to determine the clinical stage as well as blood counts and chemistries, including serum calcium, kidney function, and liver function testing. Patients with early stage or locally advanced disease are beyond the scope of this review focused solely on advanced disease.
but in general, they should have a diagnostic CT scan of the chest and abdomen, which must include the liver and adrenal glands. Those with obvious metastatic disease but no symptoms or signs suggestive of bony metastases do not need further routine imaging, such as PET/CT or radionuclide bone scan. However, because patients live longer and because treatments for brain metastases have become less invasive (e.g., stereotactic radiation), the utility of identifying asymptomatic brain metastases has become increasingly important, and MRI (preferred) or CT brain scan with intravenous contrast is recommended for all patients with stage IV NSCLC, even in the absence of symptoms.⁷

Tissue Biopsy: Does the Type of Biopsy Matter?
When approaching the patient with suspected lung cancer on imaging, the most important steps are to obtain a biopsy to make the tissue diagnosis and obtain enough tissue for histologic subtyping and biomarker testing. The American College of Chest Physicians guidelines recommend tailoring the biopsy target and method to the suspected cancer type and stage to minimize both risk and the number of procedures needed, while giving the greatest yield.⁸ A simple rule of thumb is to biopsy the most advanced site of disease. For patients with suspected lung cancer and clear mediastinal involvement (for example, bronchoscopy with transbronchial needle aspiration or endobronchial ultrasound), guided biopsy of the nodes can yield both diagnostic and nodal staging information. For patients with evidence of solitary or limited metastatic disease, it is recommended to biopsy the metastatic lesion, which both gives diagnostic material and confirms the stage. For patients with suspected malignant effusion, it is recommended to sample the fluid and if negative, proceed to pleural biopsy. For patients with multiple metastatic lesions, the most easily accessible and lowest risk lesion should be biopsied, which may include the primary tumor. It is not necessary to biopsy both the primary and metastatic lesions to help guide treatment, because biomarker testing is likely to yield similar results in both lesions.⁹

Although most of the biomarker analyses used to guide therapy in NSCLC were originally developed on surgical or core needle specimens, almost all necessary testing can be performed on both cytology and core specimens as long as they contain sufficient malignant cells.⁴,⁶,⁸ There are guidelines in place for optimizing samples obtained by endobronchial ultrasound for molecular analysis, and rapid onsite cytology evaluation is very helpful to make sure that there is enough material.⁹ Regardless of the technique used, the goal is to obtain enough material for both diagnosis and biomarker testing, while preventing the need for repeat biopsy. Bone biopsies, if decalcified, are not appropriate for molecular testing.

### Pathology Review to Determine Histologic Subtype
Historically, pathologists focused primarily on distinguishing small cell carcinoma from non–small cell carcinoma, and systemic treatments were based exclusively on this simple distinction. With the introduction of histology-restricted treatments, such as bevacizumab and pemetrexed, however, there was a clinical necessity to distinguish histologic subtypes of NSCLC.¹⁰,¹¹

In cases where the subclassification of squamous and adenocarcinoma is possible using histology or cytomorphology, no additional immunohistochemistry (IHC) testing is needed. However, when differentiation between subtypes is not possible using these tools, a panel of IHC assays should be used to help classify the subtype. Generally, TTF-1 and Napsin A are present in a majority of adenocarcinomas, whereas CK 5/6, P63, and p40 are present in most squamous cell carcinomas. To save as much tissue as possible for molecular testing, a simpler panel of TTF-1 and p40 has been suggested as sufficient for most samples, and it can be used on both pathology and cytology cell blocks.¹²

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**TABLE 1. Recommended Testing for Initial Workup of Newly Diagnosed NSCLC**

<table>
<thead>
<tr>
<th>Modality</th>
<th>Recommended Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging</td>
<td>CT scan of chest, abdomen; PET/CT scan if no distant metastases on initial imaging or if directed by symptoms; MRI or CT brain scan with contrast</td>
</tr>
<tr>
<td>Pathologic testing to determine subtype</td>
<td>TTF-1 and Napsin-A (adenocarcinoma); CK5/6, P63, and p40 (squamous cell carcinoma)</td>
</tr>
<tr>
<td>Biomarkers</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>PD-L1 IHC</td>
</tr>
<tr>
<td>Required in nonsquamous</td>
<td>EGFR mutations, ALK gene fusions, ROS1 gene fusions, BRAF mutations</td>
</tr>
<tr>
<td>Optional but recommended if NGS testing is used</td>
<td>RET gene fusions, MET exon 14 skipping mutations, MET amplification (high level), HER2 mutations</td>
</tr>
</tbody>
</table>

Abbreviation: NSCLC, non–small cell lung cancer; IHC, immunohistochemistry; NGS, next-generation sequencing.

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**PRACTICAL APPLICATIONS**
- Advanced NSCLC is a disease composed of multiple distinct subtypes defined by a variety of biomarkers, including EGFR, ALK, ROS1, MET, HER2, and BRAF as well as PD-L1.⁴
- Over 50% of patients with NSCLC will have either an actionable genomic target or high levels of PD-L1 expression within their tumors, which will dictate first-line treatment selections.⁴
- Patients with tumors having high levels of PD-L1 expression should receive first-line pembrolizumab, irrespective of histology.⁴
- Patients with tumors with low or no PD-L1 expression and squamous histology should receive chemotherapy as their first therapy, whereas patients with nonsquamous histology may receive chemotherapy alone or in combination with immunotherapy.⁴
- PD-1/CTLA-4 inhibitors represent the first novel combination of checkpoint inhibitors to be evaluated in the first-line setting for patients with NSCLC. PD-1/IDO inhibition represents a second combination strategy being investigated in phase III trials.⁴
PD-L1 Immunohistochemistry

Immune checkpoint inhibitors have become a routine part of initial and subsequent treatment of patients with advanced NSCLC, and this information is covered in a separate section of this review. Attempts to identify predictive biomarkers to better define patients who are more likely to benefit from immune checkpoint inhibitors have led to the use of PD-L1. This is the best studied biomarker so far, and it has a proven role as a predictive biomarker to decide between initial treatment with single-agent pembrolizumab or platinum doublet chemotherapy for patients with advanced NSCLC, which is discussed in detail below. In the KEYNOTE 024 trial, a randomized phase III trial of pembrolizumab versus platinum doublet chemotherapy, tumor samples were tested using the Dako 22C3 anti–PD-L1 antibody and classified based on the percentage of tumor cells that were positive (TPS). Only patients with TPS greater than or equal to 50% were enrolled on the trial. Pembrolizumab was approved for this population based on this assay, which was also approved by the U.S. Food and Drug Administration (FDA) as a companion diagnostic.\(^3\)

In addition to the 22C3 antibody, there are a number of other antibodies in use for testing for PD-L1 expression, each developed as either a companion or a complementary diagnostic tool for a different immune checkpoint inhibitor drug. They have different cutoff points for what is considered positive and which cell compartments (e.g., tumor or stroma) are evaluated. However, it is impractical for laboratories to incorporate every FDA-approved PD-L1 assay, and therefore, efforts have been made to compare the common PD-L1 assays with one another. The largest effort is the Blueprint project by the International Association for the Study of Lung Cancer, which compared four commercial anti–PD-L1 antibodies with one another on the same tumor tissue.\(^13\) The results suggest that most commercial antibodies have similar efficacy in detection of PD-L1 levels, with the exception of the SP142 antibody used as a complementary diagnostic for atezolizumab. These results were corroborated in a separate validation project by Rimm et al.\(^14\) Although the Dako 22C3 antibody is the FDA-approved companion diagnostic for pembrolizumab in the first-line treatment of PD-L1, these results suggest that any of the commercially available assays (except SP142) may be adequate for assessing PD-L1 expression.

It is recommended that every newly diagnosed patient with advanced NSCLC have PD-L1 testing done using the Dako 22C3 antibody or a validated alternative, with the goal of identifying patients with a TPS of greater than or equal to 50% expression. For patients who have already received first-line chemotherapy and are planning to proceed to second-line immune checkpoint inhibitor treatment or for patients with stage III disease who may be candidates for durvalumab, there is no clear indication that PD-L1 testing is helpful.

Other biomarkers, such as tumor mutation burden (TMB), which quantifies the number of mutations in genomic DNA and may serve as a surrogate marker for neoantigenicity, are under investigation.\(^15\) Although TMB has been shown to be associated with immune checkpoint inhibitor efficacy and seems to be independent of PD-L1 staining, it remains experimental and is not routinely recommended outside of a clinical trial.

Molecular Testing: What Is Standard of Care in 2018?

The realization that there are genetically defined subgroups of NSCLC harboring targetable alterations began in 2004 with the discovery of activating mutations in the tyrosine kinase domain of the \(EGFR\) gene in 10% to 15% of lung adenocarcinoma cases.\(^16\) This led to clinical trials showing the superiority of targeted therapies, such as gefitinib and erlotinib, in this population compared with chemotherapy, which in turn, led to recommendations in 2011 that patients with adenocarcinoma of the lung be routinely tested for \(EGFR\) mutations.\(^17\)-\(^19\) The testing was traditionally performed by Sanger sequencing, although allele-specific polymerase chain reaction–based assays eventually became more common because of increased speed and sensitivity.\(^20\)

The second validated target is \(ALK\) gene fusions, present in about 4% of adenocarcinomas. Targeted therapies against \(ALK\) first reached FDA approval in 2011 along with the companion diagnostic break-apart fluorescent in situ hybridization assay.\(^21\) In 2013, a partnership of pathology organizations (the College of American Pathologists and the Associate of Molecular Pathology) and the International Association for the Study of Lung Cancer released the first consensus guidelines on routine testing for \(EGFR\) mutations and \(ALK\) fusions in all patients with lung adenocarcinoma, regardless of smoking status or other clinical characteristics.\(^22\)

A number of other genetic alterations have now been identified in all patients with adenocarcinoma subtype. In 2016, the FDA approved crizotinib for \(ROS1\) gene fusion-positive NSCLC, and the 2017 College of American Pathologists/International Association for the Study of Lung Cancer/Associate of Molecular Pathology guidelines were updated to include routine testing for \(ROS1\).\(^23\) However, these guidelines are already outdated, because in 2017, dabrafenib and trametinib were approved for \(BRAF\) V600E mutation–positive NSCLC, which should now be included in routine testing.\(^24\) In 2018, the minimum standard for molecular testing must include these four targets (\(EGFR\), \(ALK\), \(ROS1\), and \(BRAF\)) in all patients with nonsquamous NSCLC, regardless of clinical characteristics, such as smoking history.

Although a combination of individual gene tests is adequate, the requirements for testing these targets plus PD-L1 means that many patients may have insufficient biopsy material to perform all of these assays. This will only become more difficult, because other potential targets, such as \(MET\), \(ERBB2/HER2\), and \(RET\), may become standard of care. A single multiplexed assay, such as next-generation sequencing (NGS), either in combination with fluorescent in situ hybridization or using technology that also recognizes abnormal fusion gene products would be much more reasonable from a resource perspective. For centers using NGS-based assays, guidelines recommend including other molecular targets,
because there is no additional material needed to obtain this information.4

There are also blood-based assays to detect circulating tumor DNA available for molecular testing in patients with NSCLC.20,25 However, these assays generally are less sensitive for detection of targetable genetic derangements than tissue-based assays, and therefore, negative results must be verified by tissue testing.26 For this reason, routine use of blood-based testing is not recommended, except in cases where tissue testing is not feasible or exhausted and with the caveat that a negative test may be inaccurate.

Timing Matters: Organization and Coordination Reduce Unnecessary Delays

Consults, biopsies, imaging, and pathologic and molecular testing all take time, during which the newly diagnosed patient experiences anxiety and uncertainty. Patients with lung cancer also experience the highest symptom burden among all cancer types, making the initiation of palliative treatment time sensitive.27,28 There is growing evidence that treatment delays may even impact patient survival, although the evidence is strongest in early-stage NSCLC.29,30

In recognition of the importance of timeliness in workup of patients with lung cancer, the Institute of Medicine31 and the American College of Chest Physicians have made recommendations for steps that providers should take to ensure timely care.32 In recognition of the multidisciplinary nature of lung cancer care, including surgeons, pulmonologists, medical and radiation oncologists, and palliative medicine physicians, coordination of the patient’s care should ideally use a multidisciplinary team approach to ensure better quality of care and reduce delays in treatment.33 The “ideal” time to complete workup is unknown, and every institution is unique; therefore, programs should make every attempt to track and improve their time to treatment rather than meet an arbitrary goal.

As much as possible of the workup, staging, and testing should be done in parallel rather than sequentially. For example, the College of American Pathologists/International Association for the Study of Lung Cancer/Associate of Molecular Pathology guidelines recommend that molecular testing be completed within 10 working days of ordering to be fast enough to guide initial therapy.4 However, if testing is not ordered before the oncology consult, it could introduce a delay that patients and physicians are uncomfortable with, leading to initiation of chemotherapy or other potentially less effective treatment. If molecular testing or PD-L1 IHC is ordered reflexively by the pathologist at the time of NSCLC diagnosis, the results will be available in time to influence the initial treatment discussion.

A Step Forward for Precision Medicine: FDA Approvals and Centers for Medicare & Medicaid Services Coverage

The FDA has approved the Oncomine Dx Target Test, an NGS test to detect BRAF, ROS1, and EGFR—the first NGS panel approved for the detection of multiple companion diagnostic indications. Late in 2017, the FDA approved two more profiling tests—MSK Integrated Mutation Profiling of Actionable Cancer Targets and Foundation One CDx—as broad NGS-based in vitro diagnostic tests capable of identifying several specific actionable mutations across multiple tumor indications. Foundation Medicine’s Foundation One CDx NGS platform can also use this genomic information to determine microsatellite instability and TMB, which have both been associated with response to immunotherapy. At the same time, the Centers for Medicare & Medicaid Services (CMS) proposed insurance coverage of Foundation One CDx and other similar NGS in vitro diagnostics for Medicare beneficiaries. Concurrent review by the FDA and CMS under the Parallel Review Program aims to reduce the time of FDA approval of an in vitro diagnostic and its coverage determination by CMS, providing faster access to innovative diagnostics used to guide personalized cancer care. The recent proposed national coverage determination by CMS of Foundation One CDx and other similar NGS in vitro diagnostics may help overcome the barriers associated with the use of NGS-based diagnostics and lead to the increased adoption of molecular testing in a clinical setting.34

STANDARD TREATMENT OPTIONS FOR FIRST-LINE NSCLC

New First-line Therapy Options for ALK, EGFR, and BRAF

Approximately 30% of NSCLC will have an actionable genomic target identified when molecular profiling is performed before treatment.35,36 Several randomized phase III trials have shown favorable outcomes for patients with ALK alterations and EGFR mutations receiving targeted molecular inhibitors rather than chemotherapy.17,18,37,38 Although patients with oncogene-driven cancers and their treatment opinions are outside the scope this review for “nontargetable” NSCLC, we have included, for completeness, the three new first-line treatment options available in 2018 for these patients.

The results from the global randomized phase III trial ALEX revealed a 53% decreased risk of progression or death with 600 mg of alecetinib twice a day compared with 250 mg of crizotinib twice a day in treatment-naïve patients with stage IIB or stage IV NSCLC.39 Based on these data, the FDA approved alecetinib for newly diagnosed ALK-positive NSCLC on November 17, 2017. The results from the global randomized phase III FLAURA trial also became available in 2017, comparing osimertinib, a third generation EGFR mutant–specific tyrosine kinase inhibitor (TKI), with erlotinib or gefitinib for patients with NSCLC with untreated EGFR mutant, with improved progression-free survival (PFS) and tolerability versus erlotinib and gefitinib.1 As a result of these data, osimertinib was included to the National Comprehensive Cancer Network (NCCN) compendium for first-line treatment of metastatic EGFR-positive NSCLC, with FDA approval expected in 2018. Finally, in 2017, the FDA approved the use of dabrafenib in combination with trametinib for patients with NSCLC with untreated BRAF mutant.
with NSCLC with tumors that express the BRAF V600E mutation, making BRAF V600E the fourth actionable biomarker to gain an approved therapy.40

First-Line Therapy for Patients With EGFR Mutant and PD-L1 Greater Than 50%: Targeted Therapy Trumps Immunotherapy

Small numbers of patients’ tumors will show both high levels of PD-L1 as well as a targetable oncogene, such as EGFR or ALK, after initial biomarker testing. Increasing data inform our recommendation to select a targeted inhibitor for these patients. Although small numbers of EGFR-positive patients were included in the three pivotal second-line trials comparing immunotherapy with chemotherapy that enrolled patients with nonsquamous histology, in all studies, these oncogene-driven cancers showed less benefit with immune checkpoint inhibitors compared with the patients with wild-type NSCLC studied.41–43 A recent meta-analysis compiled the results of these randomized trials and more definitively showed a lack of survival benefit for EGFR-positive patients treated with a checkpoint inhibitor, despite the well-established improvement in overall survival (OS) for wild-type NSCLC.44–46 A similar retrospective analysis, which included ALK-rearranged NSCLC, also suggests little or no benefit for oncogene drive cancers treated with immune checkpoint inhibitors.47 Thus, ensuring that all biomarker results have returned before making treatment options rather than just the first positive result is recommended.

Patients With NSCLC Are Eligible for Pembrolizumab Based on High PD-L1 Expression (PD-L1 Greater Than or Equal to 50%)

In late 2016, KEYNOTE 024 established the superiority of pembrolizumab versus platinum-based chemotherapy (median PFS: 10.3 vs. 6 months; HR 0.50; 95% CI, 0.37–0.68; p < .001) in select patients with NSCLC whose tumors expressed PD-L1 of greater than or equal to 50% defined by the IHC Dako 22C3 assay.48 Updated OS results in 2017 showed a 37% reduction in risk of death for patients treated with pembrolizumab (median OS of 30.2 months vs. 14.2 months; HR 0.63; 95% CI, 0.47–0.86; p = .002) over platinum-based chemotherapy and improvement in health-related quality of life.49,50 Based on these findings, PD-L1 testing became a requisite part of pretreatment testing to identify eligible patients with tumors expressing PD-L1 greater than or equal to 50%. Prioritizing tumor tissue for PD-L1 testing has popularized alternative methods of molecular testing, such as plasma-based testing, to obtain complete first-line diagnostic information when tissue is unavailable or has been exhausted.

Consideration of Chemotherapy With or Without Immunotherapy

At least 40% of patients with NSCLC lack an actionable driver mutation or a high level of PD-L1 expression, and for these, patients the treatment landscape is still evolving. Although

KEYNOTE 024 convincingly established anti–PD-1 monotherapy as the standard for patients with NSCLC with a TPS greater than or equal to 50%, results of CheckMate 026, a second first-line trial of almost identical design, made first-line immunotherapy more complicated for patients with lower levels of PD-L1 expression.49 Patients enrolled in CheckMate 026 had tumors expressing any level of PD-L1 expression (PD-L1 ≥ 1) and were randomly selected to receive the PD-1 inhibitor nivolumab or platinum-based chemotherapy. In the primary analysis of PFS, there was no difference between the two treatment arms (4.2 months with nivolumab vs. 5.9 months with chemotherapy; HR 1.15; 95% CI, 0.91–1.45; p = .25). The median OS was similarly negative (14.4 vs. 13.2 months; HR 1.02; 95% CI, 0.90–1.30). Although there were some imbalances in patient selection that may explain these results, even the PD-L1 high expression subset analysis showed no benefit for patients treated with nivolumab (PD-L1 ≥ 50%; HR for progression or death, 1.07; 95% CI, 0.77–1.49; overall response rate (ORR), 34% for patients with nivolumab and 39% for patients who received chemotherapy).51 Thus, it initially seemed that patients with tumors expressing PD-L1 levels 0% to 49% were still best treated first line with standard chemotherapy.

A retrospective, exploratory analysis of CheckMate 026 using whole-exome sequencing of patient tumor and blood samples (58% of the patients who were randomly selected had adequate specimens for whole-exome sequencing) measured the TMB, defined as the total number of somatic missense mutations present in a baseline tumor sample. Patients were grouped in thirds according to low TMB (1 to < 100 mutations), medium TMB (100–242 mutations), and high TMB (≥ 243 mutations). Patients whose tumors had high TMB exhibited both a higher response rate (47% vs. 27%) and an extended PFS (9.7 vs. 5.8 months) when treated with nivolumab compared with chemotherapy. There was no association between TMB and PD-L1 expression. These data suggest that TMB status may also be predictive for favorable response to frontline immunotherapy and therefore, a complementary biomarker to help identify patients who may benefit from monotherapy immunotherapy, and it is currently being evaluated prospectively in frontline clinical trials.52

Patients With Squamous NSCLC and TPS Less Than 50%: Chemotherapy Remains the Gold Standard

Histology-directed chemotherapy with or without maintenance therapy remains the gold standard for patients with tumors expressing PD-L1 0% to 49%. Patients with squamous NSCLC receive platinum paired with taxane or gemcitabine.31 For cisplatin-eligible patients, necitumumab might be considered as well, and it may be continued as maintenance beyond the four to six cycles of platinum-gemcitabine doublet.52 Carboplatin with nab-paclitaxel is an alternative regimen that was made popular by its lack of steroid premedications and weekly dosing schedule, which has higher response rates for squamous NSCLC with improved outcomes, especially for patients older than age 70.53,54
Patients With Nonsquamous NSCLC and TPS Less Than 50%: Chemotherapy With or Without Immunotherapy

For nonsquamous NSCLC, standard options continue to evolve. Patients may receive one of the standard regimens: platinum doublet with pemetrexed or platinum doublet with paclitaxel and bevacizumab. Building on the carboplatin and pemetrexed regimen, chemotherapy-naive patients with nonsquamous NSCLC in the randomized phase II KEYNOTE 021G trial received chemotherapy with or without pembrolizumab, irrespective of PD-L1 expression. Patients treated with carboplatin, pemetrexed, and pembrolizumab showed improved ORR and PFS compared with patients treated with carboplatin and pemetrexed alone, although no difference was initially observed in OS (HR 0.90; 95% CI, 0.42–1.91). Based on these results, the FDA approved the carboplatin, pemetrexed, and pembrolizumab triplet in May 2017. Although this decision was criticized by many for the fact that it was made based only one small phase II study (120 patients) and equivalent OS results, an updated OS analysis did suggest a difference had begun to emerge between the two arms (HR 0.59; 95% CI, 0.34–1.05; p = 0.0344).

Because of the controversy generated by these results and the financial implications for its widespread adoption in the front line, many have opted to wait for the confirmatory phase III KEYNOTE 189 results to become available before deciding whether to implement this newest “sea change.” Early in 2018, a press release from Merck announced that the confirmatory phase III KEYNOTE 189 met both PFS and OS coprimary endpoints. Final data and subgroup analyses by PD-L1 from KEYNOTE 189 are anticipated in the first half of 2019.

In late 2017, the results of IMpower150, a second large phase III trial evaluating patients with any PD-L1 expression level, were reported. The IMpower150 trial randomly selected patients (1,202 patients) to one of three treatment arms: atezolizumab and bevacizumab plus carboplatin and paclitaxel, atezolizumab plus carboplatin and paclitaxel, or bevacizumab plus carboplatin and paclitaxel. In contrast to all other first-line NSCLC trials to date, patients with EGFR or ALK were eligible for participation. Patients were assessed for the T-effector gene signature, which is used as a surrogate for PD-L1 expression and pre-existing immunity and defined by messenger RNA expression of PD-L1, CXCL9, and interferon gamma (IFN-γ). Patients treated with the quadruplet treatment arm had improved PFS over chemotherapy with bevacizumab (8.3 vs. 6.8 months; HR 0.61; p < .0001). A PFS benefit persisted in all subsets analyzed, including EGFR and ALK alterations, T-effector low tumors, and PD-L1–negative tumors. A trend toward an OS benefit was observed in the IMpower150 trial; however, current data analysis is immature, and further results are anticipated in the first half of 2018.

There are patients for whom first-line immunotherapy, with or without chemotherapy, may not be clinically appropriate (i.e., patients with autoimmune conditions receiving concurrent treatment with immunosuppressive agents, such as corticosteroids or disease-modifying antirheumatic drugs). Given the mechanism of action and immune-related adverse events associated with immune checkpoint inhibitors, patients with autoimmune diseases have been ineligible for immunotherapy clinical trials, and thus, our experience is quite limited. Retrospective data in patients with melanoma treated with ipilimumab and a pre-existing autoimmune condition suggest that these patients may be safely treated with immune checkpoint inhibitors. Furthermore, a retrospective analysis of Surveillance, Epidemiology, and End Results (SEER) data in patients with lung cancer and pre-existing autoimmune conditions suggests no influence on treatment patterns or increase in mortality. However, other studies suggest that these patients are at risk for higher rates of immune-related adverse events.

IMMUNOTHERAPY COMBINATION OPTIONS

Dual Immunotherapy Combinations as Frontline Treatment Options

With the success of single-agent immune checkpoint inhibitors, there is heightened interest to combine PD-1/PD-L1 inhibitors with other costimulatory or coinhibitory molecules in an effort to augment immune activation or reverse immune evasion. The majority of these trials are actively ongoing, with mature results anticipated in 2018 and beyond.

Ipilimumab and tremelimumab are two anti–CTLA-4 antibodies extensively studied either alone or in combination with other checkpoint inhibitors or with chemotherapy in NSCLC. Based on complimentary mechanisms of action at distinct immune checkpoints, combining an anti–CTLA-4 and an anti–PD-1/PD-L1 antibody is an attractive option for synergism. Moreover, clinical successes in melanoma have provided an enhanced appetite for immuno-oncology combinations in NSCLC.

Nivolumab Plus Ipilimumab

Treatment with monotherapy nivolumab results in durable response rates of approximately 15% to 20% in unselected previously treated patients with NSCLC. Ipilimumab combined with nivolumab has shown substantial activity in patients with metastatic melanoma, and it has been approved in the United States and Europe for this indication. This combination was investigated in a large multicohort phase I trial (CheckMate 012) in patients with treatment-naive metastatic NSCLC. Although a number of earlier cohorts identified doses and schedules of this combination that are too toxic for additional development, the two cohorts showing the best outcomes and tolerability were 3 mg/kg of nivolumab (N3) every 2 weeks and 1 mg/kg of ipilimumab (Ipi 1) every 6 or 12 weeks. Eligible patients were treatment-naive with metastatic or advanced-stage disease. Patients with prior treatment with oral tyrosine kinase inhibitors and evidence of disease progression were also eligible to participate. PD-L1 assessment was performed retrospectively.
### TABLE 2. First-Line NSCLC Trials With Immunotherapy Combinations With and Without Chemotherapy

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>PD-1/PD-L1 Inhibitor</th>
<th>Other IO Agents</th>
<th>Trial Name</th>
<th>Trial Title</th>
<th>Biomarker</th>
<th>Primary Endpoint</th>
<th>Primary Endpoint Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>IMpower150</td>
<td>A phase III, open label, randomized study of atezolizumab (MPDL3280A, anti–PD-L1 antibody) in combination with carboplatin plus paclitaxel with or without bevacizumab compared with carboplatin plus paclitaxel plus bevacizumab in chemotherapy-naive patients with stage IV nonsquamous NSCLC</td>
<td>Stratified by PD-L1 expression, sex (male or female), liver metastases at baseline</td>
<td>PFS and OS</td>
<td>November 30, 2017</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>IMpower131</td>
<td>A phase III, open label, multicenter, randomized study evaluating the efficacy and safety of atezolizumab (MPDL3280A, anti–PD-L1 antibody) in combination with carboplatin plus paclitaxel or atezolizumab in combination with carboplatin plus nab-paclitaxel vs. carboplatin plus nab-paclitaxel in chemotherapy-naive patients with stage IV squamous NSCLC</td>
<td>Stratified by PD-L1 expression, sex (male or female), liver metastases at baseline</td>
<td>PFS and OS</td>
<td>January 1, 2018</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>IMpower130</td>
<td>Atezolizumab (MPDL3280A, anti–PD-L1 antibody) in combination with carboplatin plus nab-paclitaxel for chemotherapy-naive patients with stage IV nonsquamous NSCLC</td>
<td>Stratified by PD-L1 expression, sex, liver metastases at baseline</td>
<td>PFS and OS</td>
<td>December 1, 2017</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>IMpower110</td>
<td>A phase III, open label, randomized study of atezolizumab (anti–PD-L1 antibody) compared with a platinum agent (cisplatin or carboplatin) in combination with either pemetrexed or gemcitabine for PD-L1–selected, chemotherapy-naive patients with stage IV nonsquamous or squamous NSCLC</td>
<td>PD-L1 TC1/2/3 or IC1/2/3; stratified by sex, ECOG status, histology, and PD-L1 expression</td>
<td>PFS and OS</td>
<td>January 17, 2019</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes; tremelimumab (anti–CTLA-4)</td>
<td>MYSTIC</td>
<td>A phase III, randomized, open label, multicenter, global study of MEDI4736 in combination with tremelimumab therapy or MEDI4736 monotherapy vs. standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC</td>
<td>Stratified by PD-L1 status and histology</td>
<td>PFS and OS</td>
<td>June 1, 2017 (PFS); mid-2018 (OS)</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes; ipilimumab (anti–CTLA-4)</td>
<td>CheckMate 227</td>
<td>An open label, randomized, phase III trial of nivolumab, nivolumab plus ipilimumab, or nivolumab plus platinum doublet chemotherapy vs. platinum doublet chemotherapy in subjects with chemotherapy-naive stage IV or recurrent NSCLC</td>
<td>Stratified by PD-L1 status (≥ 1% or &lt; 1%) and histology</td>
<td>OS and PFS</td>
<td>January 1, 2018</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>Yes; tremelimumab (anti–CTLA-4)</td>
<td>NEPTUNE</td>
<td>A phase III, randomized, open label, multicenter, global study of MEDI4736 in combination with tremelimumab therapy vs. standard of care platinum-based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC</td>
<td>Stratified by PD-L1 status, histology, and smoking history</td>
<td>OS</td>
<td>October 4, 2018</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>JAVELIN Lung 100</td>
<td>A phase III, open label, multicenter trial of avelumab (MSB0010718C) vs. platinum-based doublet as a first-line treatment of recurrent or stage IV PD-L1–positive NSCLC</td>
<td>Stratified by PD-L1 status and histology</td>
<td>OS and PFS</td>
<td>July 25, 2019</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>IMpower132</td>
<td>A phase III, open label, randomized study of atezolizumab (MPDL3280A, anti–PD-L1 antibody) in combination with carboplatin or cisplatin plus pemetrexed compared with carboplatin or cisplatin plus pemetrexed in patients who are chemotherapy naive and have stage IV nonsquamous NSCLC</td>
<td>PD-L1 all comers; stratified by sex, ECOG PS, chemotherapy type, and smoking status.</td>
<td>OS and PFS</td>
<td>November 30, 2019</td>
<td></td>
</tr>
</tbody>
</table>

*Continued...*
## TABLE 2. First-Line NSCLC Trials With Immunotherapy Combinations With and Without Chemotherapy (Cont’d)

<table>
<thead>
<tr>
<th>Trial Title</th>
<th>Key Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIRST-LINE OUTLINE</strong></td>
<td></td>
</tr>
<tr>
<td><strong>PD-1/PD-L1 Inhibitor</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Other IO Agents</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>Yes</td>
</tr>
<tr>
<td><strong>PD-L1 Status</strong></td>
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</tr>
<tr>
<td><strong>Biomarker</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>PFS</td>
</tr>
<tr>
<td><strong>Primary Endpoint Reported</strong></td>
<td>OS and PFS</td>
</tr>
</tbody>
</table>

### Table: First-Line NSCLC Trials With Immunotherapy Combinations With and Without Chemotherapy (Cont’d)

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Biomarker</th>
<th>Other IO Agents</th>
<th>Chemotherapy</th>
<th>Chemotherapeutic Regimen</th>
<th>Trial Title</th>
<th>Trial Title (Cont’d)</th>
<th>Trial Title (Cont’d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE 407</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>KEYNOTE 407</td>
<td>A randomized, double-blind, phase III study of carboplatin-paclitaxel chemotherapy with or without pembrolizumab (MK-3475) in patients with first-line metastatic squamous NSCLC (KEYNOTE 407)</td>
</tr>
<tr>
<td>PEARL</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>PEARL</td>
<td>A phase III, randomized, open label, multicenter study of durvalumab (MEDI4736) vs. standard of care platinum-based chemotherapy as first-line treatment in patients with PD-L1-positive NSCLC (PEARL)</td>
</tr>
<tr>
<td>ECHO-306</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>ECHO-306</td>
<td>A randomized, phase III study of the combination of pembrolizumab (MK-3475) plus epacadostat (INCB024360) alone or with platinum-based chemotherapy vs. pembrolizumab plus platinum-based chemotherapy plus placebo as first-line treatment in patients with metastatic NSCLC (ECHO-306)</td>
</tr>
<tr>
<td>EMPOWER LUNG</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>EMPOWER LUNG</td>
<td>A global, randomized, phase III, open label study of REGN2810 (an anti-PD-L1 antibody) vs. platinum based chemotherapy in first-line treatment of patients with advanced or metastatic NSCLC (EMPOWER LUNG)</td>
</tr>
<tr>
<td>POSEIDON</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>POSEIDON</td>
<td>A phase III, randomized, multi-center, open label, comparative global study to determine the efficacy of durvalumab or durvalumab plus tremelimumab in combination with platinum-based chemotherapy for first-line treatment in patients with metastatic NSCLC (POSEIDON)</td>
</tr>
<tr>
<td>NCT03191786</td>
<td>PD-L1 ≥ 25%; stratified by PD-L1 expression, histology, and smoking status</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>NCT03191786</td>
<td>A phase III, open label, multi-center, randomized study to investigate the efficacy and safety of atezolizumab compared with chemotherapy in patients with treatment-naive advanced, recurrent (stage IIIB not amenable for multimodality treatment), or metastatic (stage IV) NSCLC who are deemed unsuitable for platinum-containing therapy (NCT03191786)</td>
</tr>
<tr>
<td>CheckMate 9LA</td>
<td>PD-L1 ≥ 25%; stratified by ECOG status, geographic region, and histology</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>CheckMate 9LA</td>
<td>A phase III, randomized study of nivolumab plus ipilimumab in combination with chemotherapy vs. chemotherapy alone as first-line therapy in stage IV NSCLC (CheckMate 9LA)</td>
</tr>
<tr>
<td>KEYNOTE 598</td>
<td>PD-L1 ≥ 25%; stratified by ECOG status, geographic region, and histology</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>KEYNOTE 598</td>
<td>A phase III, randomized study of nivolumab plus ipilimumab in combination with chemotherapy vs. chemotherapy alone as first-line therapy in stage IV NSCLC (KEYNOTE 598)</td>
</tr>
<tr>
<td>CheckMate 654</td>
<td>PD-L1 ≥ 25%; stratified by ECOG status, geographic region, and histology</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>CheckMate 654</td>
<td>A phase III, randomized, double-blind study of pembrolizumab (MK-3475) plus epacadostat (INCB024360) vs. pembrolizumab plus placebo as first-line treatment in patients with metastatic NSCLC (CheckMate 654)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy; NSCLC, non–small cell lung cancer; OS, overall survival; PFS, progression-free survival; PS, performance score.
and was not used for randomization. As reported by Hellmann et al., 78 eligible patients were treated; 77 were considered evaluable, and one patient never received treatment after randomization.

The primary endpoint of this phase I study was safety as defined by the frequency of adverse events. Secondary endpoints included clinical efficacy, median duration of response, and PFS at 24 weeks according to RECIST version 1.1. Median duration of follow-up was about 12 months in the N3/Ipi 1 every 6 weeks group and about 13 months for the N3/Ipi 1 every 12 weeks group. Objective response rate was 47% in the every 12 weeks group and 38% in the every 6 weeks group. There were no complete responses. In addition, 32% in the N3/Ipi 1 every 12 weeks arm and 18% in the N3/Ipi 1 every 6 weeks arm had stable disease. The median duration of response was not reached in either group, and at the time of reporting, the 24-week PFS rates were 68% and 47% in the every 12 weeks and every 6 weeks groups, respectively.

Treatment-related adverse events of any grade occurred in 82% of the N3/Ipi 1 every 12 weeks cohort and 72% of the N3/Ipi 1 every 6 weeks group. The rates of grades 3 or 4 treatment-related adverse events were 37% and 33% in the every 12 weeks and every 6 weeks cohorts, respectively. As expected, these events included skin, gastrointestinal, endocrine, and pulmonary events. Overall, the most frequent grade 3 or 4 adverse event was lipase elevation, which was seen with a frequency of 8% in the every 12 weeks group. Pneumonitis was reported in two patients (5%) in the every 12 weeks group and only one patient (3%) in the every 6 weeks cohort. Serious adverse events were seen in 32% and 28% of the 12 and 6 weeks groups, respectively. The extent of clinical benefit correlated with PD-L1 expression. Patients with greater than or equal to 50% tumor PD-L1 expression had a response rate of 92%, although this sample size is very small (13 patients). Responses were also reported in both smoker and nonsmoker groups, although higher rates were seen in the current of former smokers (46% vs. 27%).

The multiarm phase III two-part study, CheckMate 227, continued to explore the use of nivolumab in the frontline setting for patients with advanced NSCLC. In part 1, patients with PD-L1 expression greater than or equal to 1% were randomized to N3 every 2 weeks plus Ipi 1 every 6 weeks, 240 mg of nivolumab as a flat dose every 2 weeks, or chemotherapy. Patients with PD-L1 expression less than 1% were randomly selected to receive N3 every 2 weeks plus 1 mg/kg of Ipi every 6 weeks, 360 mg of nivolumab as a flat dose every 3 weeks plus chemotherapy, or chemotherapy alone. In part 2, previously untreated patients, irrespective of PD-L1 expression, were randomly selected 1:1 to receive histology-directed platinum doublet chemotherapy alone or in combination with 360 mg of nivolumab every 3 weeks. Part 2 is currently ongoing; however, part 1 has completed accrual. A recent press release by BMS reported that the combination of nivolumab and ipilimumab showed superior PFS over chemotherapy in patients with a high TMB (≥ 10 mut/mb).

Durvalumab Plus Tremelimumab

Following a similar rationale, durvalumab plus tremelimumab is another immuno-oncology combination being extensively studied. Also part of a phase I clinical trial, patients with locally advanced or metastatic NSCLC were treated with durvalumab, an anti–PD-L1 antibody, in doses of 3, 5, 10, 15, and 20 mg/kg every 4 weeks or 10 mg/kg every 2 weeks and tremelimumab, a CTLA-4 blocker, at 1, 3, and 10 mg/kg every 4 weeks for six doses followed by three additional doses every 12 weeks. The primary endpoint of this trial was safety and tolerability.

As reported by Antonia et al., 70 102 eligible patients were enrolled in this trial with PD-L1 expression assessed using the validated SP263 antibody. Samples were deemed positive if 25% or more of the tumor cells showed membranous staining for PD-L1. Patients in this study had to be immunotherapy naïve but could have had any number of prior therapies. Measurable disease by RECIST 1.1 was required at enrollment. The dose escalation followed a standard 3 + 3 design, with treatment given for 12 months or until disease progression.

Dose-limiting toxicity was observed in the group receiving durvalumab at 20 mg/kg every 4 weeks and tremelimumab at 3 mg/kg (one grade 3 elevated aspartate aminotransferase and alanine aminotransferase and one grade 4 increase in lipase). The most common treatment-related adverse event as reported by the investigators were diarrhea (32%), fatigue (24%), and pruritus (21%). The most common grade 3 or 4 adverse events were diarrhea (11%), colitis (9%), and increased lipase (8%). In general, these adverse events were manageable. Based on the safety and efficacy data, 20 mg/kg of durvalumab every 4 weeks and 1 mg/kg of tremelimumab were chosen for the dose expansion phase of the trial. Three treatment-related death were reported in various cohorts: one each caused by myasthenia gravis, pericardial effusion, and a neuromuscular disorder. Response data were reported in 63 evaluable patients who had completed at least 24 weeks of follow-up. An objective response rate was reported in 17% of patients, and a disease control rate was reported in 29%. In the group with a confirmed objective response rate, the median time to response was 7.1 weeks. Median duration of response was not reached. In a post hoc analysis of 58 patients enrolled in this trial with wild-type EGFR or ALK status, the objective response rate was 19%.

A multiarm phase III trial (MYSTIC) that includes this combination (20 mg/kg of durvalumab with 1 mg/kg of tremelimumab) every 4 weeks versus single-agent durvalumab every 4 weeks versus investigator choice platinum doublet chemotherapy has completed accrual. A press release in July 2017 indicated that this combination failed to show improvement in PFS compared with the control arm of the trial in patients with tumors expressing PD-L1 greater than or equal to 25%. Details of this analysis have not yet been
Indoleamine 2,3 dioxygenase (or IDO) is an enzyme in the tryptophan catabolic pathway that seems to play a central role in tumor progression. IDO activation can suppress T and natural killer (NK) cells and generate and activate T regulatory cells in addition to myeloid-derived suppressor cells. Epacadostat is an IDO inhibitor that has been combined with a number of anti–PD-1 antibodies in an attempt to increase tumor response rates. The combination of this agent at a variety of doses plus a flat dose of 200 mg/kg of pembrolizumab was evaluated in a phase I/II trial in patients with advanced malignancies (ECHO-202/KEYNOTE 037). A dose of 100 mg of epacadostat twice a day and 200 mg of pembrolizumab every 3 weeks was selected for the phase II portion of the trial, in which patients with NSCLC (40 patients) with no to two prior lines of therapies and therapies of progression were treated on this protocol. A response rate of 35% and a disease control rate of 63% were reported in 25 patients included in the efficacy analysis. Most of these responses were durable, with a median duration of 26.9 weeks as of the cutoff date for this analysis. Responses were higher in patients with PD-L1 TPS greater than or equal to 50%.

The most frequent treatment-related adverse events reported were fatigue (28%), arthralgia (17%), nausea (14%), decreased appetite (10%), pruritus (10%), and rash (10%). Grades 3 and 4 treatment-related adverse events were elevations in lipase (three patients), fatigue (two patients), and rash (two patients). Phase III trials of this combination are now ongoing.

The intense interest and excitement that immunotherapy has generated have led to a proliferation of multiple clinical trials with various drugs capable of modulating different aspects of the immune system (Table 2). The costimulatory and coinhibitory pathways targeted carry their own potential risks and potential promise of activity. Rationally designed trials that take advantage of the additive or synergistic potential of new combinations are essential in determining which approach has the best clinical efficacy with the lowest toxicity profile. Given the complexity of the immune system, these approaches must selectively target any number of immune escape mechanisms used by the tumors. These include ways to alter the tumor microenvironment to allow better T-cell infiltration; downregulation of T regulatory cells, myeloid-derived suppressor cells, or other inhibitory cells; and activation of any number of costimulatory pathways or inhibition of others. As investigators, we also must avoid the mistakes that we have made in the past by simply combining an active drug with anything that we feel might be effective without a careful examination of the rationale or adequate preclinical data. An area that has not been explored to date is the simple question of sequencing of treatments. This concept of determining if there is a sequence of treatment that could be most beneficial can be explored in trials with simple designs and over a relatively short period of time (Tables 1 and 2).

CONCLUSIONS

Biomarker discovery has fueled an ever-expanding appreciation of NSCLC as many diseases with distinct natural histories and clinical phenotypes. In parallel, an explosion of new therapeutic strategies have afforded unprecedented treatment choices for clinicians and their patients. It has never been more complicated to assign frontline treatment of NSCLC. We hope that oncologists will use this review as an algorithm to help select the most appropriate testing and potentially life-altering therapies for their newly diagnosed patients with NSCLC.

References


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Although tissue biopsies play a key role in NSCLC care and have a range of purposes, blood-based diagnostics in some instances offer the potential to noninvasively provide similar, clinically useful information. Lung cancer accounts for more cancer-related deaths in the United States than any other type of cancer.1 The management of lung cancer, particularly NSCLC, has evolved tremendously over the last 15 years. Among solid tumor cancers, NSCLC management has become a prominent example of precision medicine. Clinical management of NSCLC now depends on surgical, chemotherapeutic, and radiation treatment regimens based on pathologic findings and clinical staging as well as targeted therapies based on molecular profiling. As molecular testing becomes increasingly important, preserving tissue for this purpose while rendering an accurate histologic diagnosis becomes a key consideration, particularly in advanced-stage NSCLC, in which small biopsy samples or aspirates are often the only specimen available. Next-generation sequencing panels are a powerful method of providing information relevant for both standard-of-care and investigational treatment options. However, taking advantage of the abundance of information gleaned from these panels requires careful annotation, prioritization, and reporting of molecular findings and their clinical significance. Although molecular profiling has traditionally relied on direct sampling of neoplastic tissue, blood-based diagnostics now offer the potential to provide some clinically useful information noninvasively.

PATHOLOGY AND STAGING
Pathologic evaluation of clinically identified lesions remains the gold standard for diagnosing malignancy. When tumors are excised, assessing pathologic stage is critical. In NSCLC, pathologic stage persists as the single best prognostic consideration, and the components of pathologic stage are the building blocks of determining clinical stage. Most pathologic assessment is performed on the basis of microscopic review of hematoxylin and eosin–stained slides, with specific criteria used to assess the tumor type, subtypes (as appropriate), pathologic stage, and any other key findings. Immunohistochemistry (IHC) is frequently used as an adjunct to hematoxylin and eosin review and can help to further characterize a lesion and refine the diagnosis. In some cases, IHC is necessary to determine the proper classification of a tumor.

Increasingly, pathologists view the approach to classification of pulmonary lesions as distinct according to the type of sampling procured. The approach to small samplings, such as fine-needle aspiration, bronchoscopic biopsy, and endobronchial ultrasonography–guided fine-needle aspiration, is markedly different from how a pathologist begins to assess a resected specimen.5 For example, the finding of squamous carcinoma on a small biopsy sample does not exclude the possibility that this represents a partial sampling of an adenosquamous carcinoma, which has a probability of targetable alterations similar to that of adenocarcinoma.6 This is of particular and growing importance: Small samplings are often the only tissue specimens procured from patients with advanced-stage NSCLC because they will likely not proceed to surgical resection. Importantly, balancing the needs to fully classify the lesion with the need to preserve material for molecular and other biomarker testing has become a paramount consideration in the daily workflow for pathologists who manage these small specimens.
**Tumor Classification**

Pulmonary tumors are best classified by using the World Health Organization (WHO) system, which was revised in 2015.4-7 The approach indicated by the new WHO classification system places increased importance on the use of IHC, including for complete characterization of resected lesions. This classification also codified some of the differences in approach and nomenclature for the consideration of small samplings versus resection samples.

The overriding goal of pathologists should be to define, whenever possible, the histologic type of tumor present in a sample deemed to be malignant. In resection samples, the availability of abundant materials can make this more straightforward; however, in small samplings, extensive characterization by IHC or other modalities can interfere with preserving tissue for molecular characterization for therapeutic decision-making. The WHO classification divides epithelial tumors first and foremost into NSCLC and small cell lung cancer.4-7 This is largely a historically derived nomenclature; in 1926 Barnard published findings suggesting that "oat cell carcinoma," as it was then known, should be considered a bronchogenic carcinoma rather than a lymphomatous or sarcomatous lesion as had been previously thought.6,9 As the study of lung tumors advanced, it became clear that this type of tumor was distinct from other lung tumors, leading to this classification of "small cell carcinoma" and "non–small cell carcinoma," which remains in use today. Further discussion of small cell lung cancer is beyond the scope of this article.

NSCLC collectively describes numerous epithelial-derived tumors, of which the two most common histologic types are adenocarcinoma and squamous cell carcinoma. Other histologic types are varied and typically rare, such as large cell carcinoma, pleomorphic carcinoma, and salivary gland–like tumors of the lung. Proper identification of the appropriate histologic type is important because it affects prognosis and, in many cases, therapy selection as well as considerations for molecular testing.10,11 For example, the role of tumor genotyping in pure squamous carcinoma is debated, whereas genotyping is recommended for all advanced nonsquamous NSCLC. In numerous circumstances, IHC is paramount in determining the correct histologic type. In particular, the solid variant of adenocarcinoma has substantial morphologic overlap with nonkeratinizing squamous cell carcinoma, and IHC can be crucial in making the distinction.15 This can typically be achieved by using a minimal set of IHC markers, consisting of a single adenocarcinoma and squamous marker, such as TTF-1 and p40.12,13 The diagnosis of squamous cell carcinomas that do not have keratinization should be confirmed with squamous IHC markers.9

An important change in the reporting of invasive adenocarcinoma is the recommendation to include characterization of the histologic subtypes, which include lepidic, acinar, papillary, solid, and micropapillary and may correlate with histologic grade.14 The recommendation has been made to characterize lesions according to the predominant subtype and estimate the percentage of various subtypes in 5% increments. There is some evidence that the tumor subtype may be associated with prognosis in patients with early-stage resected disease, with the presence of higher-grade histologic types (micropapillary and solid) being associated with a higher incidence of occult lymph node metastases.15,16 In clinical practice, however, the predominant subtype of adenocarcinoma does not currently affect therapy decisions, and the clinical application of determining subtype has not been established in advanced-stage disease.

**Staging**

In 2017, the American Joint Commission on Cancer published the eighth edition of the *Cancer Staging Manual*, which included several updates to the criteria used for staging of NSCLC.17,18 Key differences between the two versions include an additional tier of early-stage disease (T1c), reclassification of lesions greater than 5 cm but 7 cm or less in greatest dimension as T3 (in place of T2), and reclassification of tumors greater than 7 cm in greatest dimension as T4 (instead of T3). These and other revised staging criteria have become incorporated into routine practice, but some of the changes, particularly in synoptic reporting, may be unfamiliar to practicing oncologists. For example, spread through air spaces is now an optional component of the pathologic staging synoptic report, and its presence portends a higher risk for recurrence in tumors treated with limited resection.19-21 Another substantial change in the staging system includes separate measurements of invasive and lepidic components in adenocarcinoma. An additional area addressed directly in the new staging approach is classification of multifocal disease for the consideration of separate primary tumors versus intrapulmonary metastases, using a predominantly histologic-based approach.17,18,22 Growing evidence suggests that molecular testing can be a useful approach to determining the clonal relationship between multiple tumor nodules.14,23,24

**Specimen Management**

Numerous logistical issues are also of note when the multiple priorities assigned to diagnostic small samplings of NSCLC are being considered. As noted, the need to balance...
IHC characterization (including consideration of metastases from nonlung sites) with preservation of material for molecular testing can be challenging, and numerous approaches can aid in the preservation of tissue.25 Given the clinical urgency in tumor classification and molecular testing in cases of advanced NSCLC, an understanding of the timelines for the technical and interpretive processes in pathology can aid in planning for individual patients. Histologic processing of biopsy samples is typically accomplished in 1 business day, allowing for a preliminary assessment of a sample on the following day. IHC staining can add 1 to 3 days or more to total assessment time, particularly if staining is done in stages to minimize tissue use for classification. Often, molecular testing is not initiated until the histologic assessment is complete, in case material is needed for additional IHC.

MOLECULAR PROFILING

Standard-of-Care Molecular Biomarkers in NSCLC

The current guidelines from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology recommend evaluation of EGFR, ALK, and ROS1 on all patients with lung cancer patients who have metastatic nonsquamous disease, irrespective of clinical characteristics.3 These guidelines do not recommend other genes, including BRAF, KRAS, RET, ERBB2 (HER2), and MET, as routine stand-alone assays outside the context of a clinical trial; however, in the United States a combination therapy is approved for patients with NSCLC who have BRAF p.V600E mutation, which may raise the impetus to consider a stand-alone assay for this target. Of note, multiplexed genetic sequencing panels are preferred over multiple single-gene tests to identify other treatment options beyond EGFR, ALK, and ROS1. For laboratories performing next-generation sequencing (NGS), it is recommended that BRAF, KRAS, RET, ERBB2, and MET be included. The National Comprehensive Cancer Network (NCCN) guidelines have one or more specific treatment recommendations for all of the genes except KRAS.3 These targeted therapies are indicated for patients with NSCLC who have metastatic disease with sensitizing molecular alterations. Tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib, afatinib, and osimertinib are all U.S. Food and Drug Administration (FDA)–approved for the treatment of both EGFR exon 19 deletions and EGFR L858R mutations, whereas osimertinib is the only TKI approved for the treatment of commonly acquired resistance mutation p.T790M, and afatinib is the only TKI approved for uncommon EGFR driver mutations (e.g., G719X, L861Q). Crizotinib is FDA-approved for the treatment of NSCLC with an ALK or ROS1 rearrangement. Alectinib, ceritinib, and brigatinib are also approved for ALK-rearranged NSCLC. The combination of BRAF inhibitor dabrafenib and MEK inhibitor trametinib was recently approved for NSCLC with BRAF p.V600E. The anti–programmed cell death ligand 1 (PD-L1) antibody pembrolizumab is FDA-approved for NSCLC as a first-line therapy for high PD-L1 expression (tumor proportion score ≥ 50%) in the absence of an EGFR mutation or ALK rearrangement. This drug is also approved for patients who have progressed while receiving platinum-based chemotherapy or patients with EGFR or ALK alterations who have progressed while receiving an FDA-approved targeted therapy, with a tumor proportion score of 1% or greater. The NCCN guidelines also recommend consideration of emerging targeted therapeutic options, including crizotinib for MET exon14 skipping mutations or high-level MET amplification, cabozantinib or vandetanib for RET rearrangements, and ado-trastuzumab emtansine for ERBB2 mutations. The NCCN guidelines also point out that KRAS is associated with poorer prognosis and reduced responsiveness to EGFR tyrosine kinase inhibitor therapy, and that the presence of a KRAS mutation may identify patients who will not benefit from further molecular testing (owing to the low probability of overlapping targetable variants). Variants affecting many other potentially targetable genes are being evaluated in various clinical trials, including FGFR1 amplification, FGFR3 fusions, NTRK1 fusions, and PIK3CA and AKT1 mutations. NGS testing is increasingly enabling routine evaluation of those genes, as recommended by national guidelines, as well as many that are being evaluated in these trials.

Next-Generation Sequencing Panels

NGS is a powerful tool that enables the simultaneous interrogation of many regions of human genome. In evaluating NSCLC samples, a wide array of information can be collected in a single test. This information may be relevant for standard-of-care treatment with FDA-approved drugs; off-label use of FDA-approved drugs based on clinical practice guidelines, clinical studies, and/or preclinical data; or consideration for enrollment in a clinical trial. Other information will have no immediate clinical utility, but panels often include targets without immediate clinical utility based on the possibility that such information may be useful in the future. As the volume of data from NGS testing grows, so does the challenge of separating findings that are clinically meaningful and prioritizing their clinical utility. Molecular pathologists—in collaboration with their oncology colleagues—are tasked with evaluating this abundance of data, distilling down to what is clinically relevant, and communicating this information in the most cogent and manageable manner possible. A general algorithm for NGS data analysis can be illustrated as in Fig. 1.

Filtering Variants of No Clinical Utility

A great deal of information generated from NGS data is of no clinical utility and should not be reported because doing so would only make extracting clinically useful information that much more difficult for all practitioners. These unreportable
findings include artifacts, synonymous variants, most intronic variants (other than splice site mutations and functional gene rearrangements), and benign germline polymorphisms.

The distinction between germline and somatic variants is not always clear (unless nonneoplastic tissue is also evaluated), and some germline variants can be clinically relevant, including those associated with cancer predisposition syndromes. Without a tumor-normal comparison, distinguishing somatic from germline variants relies largely on constitutional databases (such as 1000 Genomes Project, ExAC, dbSNP, ClinVar) and cancer-specific databases (Catalog of Somatic Mutations in Cancer [COSMIC], cBioPortal). However, information from these databases must be interpreted with caution because some somatic variants (e.g., JAK2 V617F) are included in germline databases and both deleterious and benign (e.g., KIT M541L) are included in cancer-specific databases. Primary literature may also be helpful in some instances. For example, even the acquired resistance mutation EGFR p.T790M can be seen rarely as a germline event, and this must be considered when identified at cancer diagnosis.

Somatic variants are frequently inferred to represent driver or passenger mutations. A driver mutation is one that confers a selective growth advantage for the mutated cell, whereas a passenger mutation has no growth advantage and is observed within a tumor because of its co-occurrence with a driver. Because passenger mutations are random events that are not selected for during oncogenesis, they generally are not recurrent, whereas driver mutations are. Therefore, the frequency of a particular variant within somatic mutations databases such as COSMIC and cBioPortal and the large cancer-specific studies (e.g., TCGA) are eminently useful in evaluating the potential oncogenesis of a mutation. Functional studies provide the most definitive evidence of oncogenesis; however, they are rarely available for unusual alterations, and identification of functional studies in the literature can be laborious. Although driver mutations are generally the most clinically relevant, passenger mutations may also be informative. For example, several studies have demonstrated a correlation between tumor mutation burden and response to immune checkpoint inhibitor therapies.

**Classification of Variants**

Whole-genome studies have demonstrated a median of 888 and 15,659 mutations in NSCLC samples from nonsmokers and smokers, respectively. As described above, only a subset of these mutations represent driver mutations and only a tiny subset of these mutations offer potential clinical utility. Most molecular laboratories perform panel-based NGS that restricts evaluation to those genes or gene regions with recurrent driver mutations and potential clinical significance. However, even smaller, targeted panels can identify several mutations in a single sample. Classification of variants based on clinical significance based on availability of relevant therapies, national guidelines, and clinical/preclinical studies facilitates prioritization of molecular findings and appropriate clinical management.

Several classification schemas are used by various institutions performing clinical sequencing. MD Anderson Cancer Center’s Knowledge Base for Precision Oncology classifies therapies on the basis of the level of clinical or preclinical evidence supporting its efficacy for a particular tumor type and a particular type of variant. Other groups also incorporate clinical trial eligibility criteria. Guidelines for the interpretation and reporting of sequence variants in cancer were recently published in a joint consensus recommendation from the Association for Molecular Pathology, ASCO, and College of American Pathologists. These guidelines recommend grouping clinical and
experimental evidence into four levels based on therapeutic, diagnostic, and/or prognostic significance.

Other Variant-Specific Information
Most clinical NGS reports describe each clinically significant variant. Descriptions often include the following:

- A precise, unambiguous description of each clinically significant variant. This is essential. A single variant can be designated in many different ways depending on variant nomenclature, the reference transcript being used, and other factors. The College of American Pathologists requires reporting of sequence variants by using Human Genome Variation Society nomenclature to include the gene name based on the HUGO Gene Nomenclature Committee, a standard versioned reference identifier to the transcript/protein, the reference genome assembly and version number, and chromosomal position.
- The expected functional effect of the variant (predicted or based on functional studies) illustrating that the variant is truly a driver mutation. For example, EGFR L858R mutations result in constitutive activation of EGFR and downstream growth signaling.
- A statement indicating whether the variant (or similar variants) has been described in the tumor type being evaluated, possibly with an estimate of the relative frequency.
- Prognostic significance (if any). For example, KRAS mutations have been associated with an inferior prognosis in NSCLC.
- Patterns of mutual exclusivity. For example, KRAS mutations are generally mutually exclusive with many other targetable molecular alterations. As a result, a KRAS mutation may indicate patients who will not benefit from further molecular testing.
- Therapeutic implications, including FDA-approved indications, off-label therapeutic options, and therapies being investigated in clinical trials. The available evidence supporting or refuting the observed variant (or similar variants) being predictive of drug response should be summarized and appropriately cited.
- The effect of other variants also identified. For example, although an EGFR exon 19 deletion is associated with responsiveness to first-generation EGFR inhibitors, such as gefitinib, a co-occurring EGFR T790M mutations is associated with resistance.
- The types of variants detected including single nucleotide variants, insertion/deletion mutations, copy number variants, gene fusions, and gene expression. This is an important consideration a report is being interpreted. For example, a panel that includes MET sequencing for mutations may not provide information about MET amplification (copy number variants).
- Types of variants that may not be detected. For example, an amplification-based NGS that relies on primers targeting known gene fusions may fail to detect fusions involving novel or poorly described fusion partners or unusual fusion transcripts.

BIOPSY VERSUS LIQUID BIOPSY
The Role of Biopsies and Liquid Biopsies
The fundamental role of pathology in lung cancer care is inherently tied to a fundamental role for tissue biopsies. However, the invasive nature of tissue biopsies has led to interest in noninvasive ways of obtaining the same information. Such noninvasive blood-based diagnostics are sometimes termed “liquid biopsies.” Although a range of blood-based diagnostics are being studied, the best-established and most widely used technologies study free-floating DNA within the plasma (cell-free DNA [cfDNA]). This represents an intuitive extension of tumor analysis wherein DNA-based biomarkers represent some of the most transformative diagnostics in the care of NSCLC. Here we review the various roles that biopsies play in lung cancer care and the potential for plasma cfDNA genotyping to serve as an alternative.

The Diagnostic Biopsy
The initial diagnostic biopsy is essential in that it establishes the diagnosis of malignancy and allows for histologic typing, as discussed previously. Patients and oncologists both rely on the certainty of a pathologic diagnosis when planning cancer care and are reluctant to initiate cancer treatment without it; thus, it is a type of biopsy that noninvasive methods may never come to replace. It must be acknowledged, however, that there are instances where comorbidities preclude biopsy and treatment must be considered based upon a presumed diagnosis of lung cancer. For example, radiotherapy is at times performed on early-stage lung cancer in the absence of pathologic proof, an approach that comes with some risk for overtreatment. One could similarly envision scenarios where a patient presents with a lung mass and metastases to bone, brain, or liver and the patient is too ill for a diagnostic biopsy. If plasma genotyping in that instance detected a mutation that is largely pathognomonic for lung cancer (e.g., an EGFR mutation or ALK fusion), one could consider empirical targeted therapy for presumed lung cancer. But in such a case, pathologic confirmation should still be pursued should the patient’s condition improve.

The Staging Biopsy
In planning curative therapy for lung cancer, staging biopsies, such as mediastinal lymph node biopsies or biopsies of suspected metastatic sites, are routine. Because staging imaging
studies (PET, MRI) are imperfect, biopsies are a common supplement. For example, in a patient with an isolated rib lesion on PET, fine-needle aspiration of the bone lesion can confirm metastatic disease and inform prognosis. Plasma genotyping could eventually play a similar orthogonal role in evaluating for the presence of disease spread. Across several data sets, it is apparent that detection in cfDNA of a previously identified tumor genotype (a marker of cancers that shed DNA into the plasma) is a marker of a relatively poor prognosis. One could envision that detection of tumor DNA within the plasma cfDNA could similarly be a marker of poor prognosis in early-stage lung cancer, informing the chance of cure and contributing to cancer staging. This is a question that deserves further study in prospective data sets.

**The Biopsy to Assess for Residual Disease**
Neoadjuvant therapy is one of several standard management strategies in planning multimodality therapy for locally advanced NSCLC. One reason neoadjuvant therapy is attractive is that it permits the testing of the resection specimen for degree of pathologic response. Many studies have now shown that a major pathologic response, defined as at least 10% residual viable tumor in resected lung and lymph node tissue, portends a much better postoperative prognosis, whereas the presence of greater than 10% residual tumor confers a higher risk for recurrence. Plasma cfDNA genotyping may also offer an opportunity for detection of residual active cancer, as initially shown in a prospective cohort of 230 patients with resected stage II colon cancer, where the 8% of patients with detectable tumor mutations in plasma cfDNA postoperatively had a dramatically worse recurrence-free survival (hazard ratio, 18). This was also studied in a mixed cohort of stage I to III NSCLC and small cell lung cancer receiving curative therapy. Of 32 patients with plasma available within 4 months of completing therapy, 17 (53%) had detectable tumor mutations in plasma cfDNA, and these patients had a dramatically higher rate of recurrence. Although currently available clinical assays for plasma genotyping are unlikely to be suitable for detection of residual disease, this is a future application that deserves prospective study.

**The Recurrence Biopsy**
Cancer recurrence after attempted curative therapy is a dramatic moment for a patient with lung cancer because recurrence often indicates that their cancer is no longer curable. Given the seriousness of lung cancer recurrence, biopsy to pathologically confirm recurrence is standard for patients more than 6 to 12 months out from curative therapy. As discussed above for diagnostic biopsies, a noninvasive assay in some cases might serve as an alternative in patients with lung cancer too sick to undergo a recurrence biopsy. This would make the most sense in patients whose definitively treated lung cancer was known to harbor a pathognomonic lung cancer genotype (e.g., an EGFR mutation or ALK fusion). If this variant were detected in plasma at time of suspected recurrence, a trial of targeted therapy could serve as an alternative to biopsy, confirming recurrence. Similarly, if the pretreatment genotype is known, the presence of those markers could serve a similar purpose, although caution is warranted if the alteration is common to multiple malignancies (such as KRAS or TP53 mutations).

**The Biopsy for Genotyping**
It is well established that diagnostic lung cancer biopsies are frequently inadequate for the range of molecular studies now needed for treatment decisions, such as PD-L1 IHC and NGS. The diagnostic specimen may be small and much of the tissue could be exhausted during the performance of necessary studies to determine the diagnosis and histologic subtype. For this reason, a repeat biopsy is commonly required to permit complete molecular testing. Plasma cfDNA genotyping is an intuitive noninvasive option for such patients who are planning an additional biopsy. In 2016 the FDA approved the first plasma cfDNA genotyping assay for detection of EGFR mutations in patients with NSCLC who did not have tumor tissue available for genotyping. Furthermore, broader genotyping of a range of oncogenic drivers in cfDNA is now possible with commercially available plasma NGS technologies. Still, the sensitivity of plasma genotyping for driver mutations present within the tumor is only in the range of 60% to 80%. This means that negative plasma genotyping results must reflex to a biopsy for tumor genotyping. In some cases, it may be worth concurrently scheduling a biopsy procedure while waiting for plasma genotyping results because this shortens the time interval to molecular testing in the event of a negative plasma genotyping report.

**The Response Biopsy**
Biopsy at time of treatment response is not part of routine clinical practice but is increasingly used in some clinical trials to assess treatment effect. The aim is usually to assess a pharmacodynamic marker, such as adequate inhibition of a target, although tumor analysis is not always possible when a dramatic treatment effect results in little residual tumor for analysis. Plasma genotyping on therapy also can permit a noninvasive measurement of treatment effect. Many highly active targeted therapies can induce a rapid clearance of driver mutations from the plasma cfDNA, which is associated with a more favorable outcome. The clinical and scientific implications of such a plasma response still require further investigation.

**The Resistance Biopsy**
Biopsies for genotyping of lung cancer drug resistance have more recently emerged as a standard of care since the FDA approval of osimertinib for EGFR-mutant lung cancer and acquired drug resistance mediated by a specific resistance mutation, EGFR p.T790M. And yet, such resistance genotyping has long been used for clinical trial enrollment given the range of potentially targetable resistance mechanisms in EGFR-mutant lung cancer. Furthermore, such resistance biopsies are increasingly common as targetable resistance mechanisms can be seen with other targeted therapies, such as ALK and MET inhibitors. The convenience of plasma cfDNA genotyping makes it an ideal technology for testing for
many of these resistance mechanisms, such that it is now an established standard for EGFR p.T790M testing in patients reluctant to pursue a resistance biopsy. However, as with initial genotyping, sensitivity is imperfect and a negative plasma result must reflex to a biopsy for tumor genotyping.

CONCLUSION

Precision medicine is exemplified by NSCLC in which management is tailored based on pathologic findings, clinical staging, and molecular profiling. Next-generation sequencing panels enable molecular profiling that includes information relevant for both standard of care and investigational treatment options. Taking full advantage of this abundance of information requires careful annotation, prioritization, and reporting of molecular data. Preserving tissue for molecular testing while rendering an accurate histologic diagnosis has also become a key consideration for pathologists and oncologists. Blood-based diagnostics now offer the potential to also provide clinically useful information noninvasively.

References


Dedicated attention to the palliative and supportive care needs of patients with lung cancer is now the standard of care as reflected in national and international guidelines, including those of ASCO, the European Society for Medical Oncology, and the National Comprehensive Cancer Network. Palliative and supportive care is defined as patient- and family-centered care that optimizes quality of life (QOL) by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs and facilitates patient autonomy, access to information, and choice. Resultant to proliferation of guidelines, palliative care specialty services are now increasingly available and have become more routinely integrated into multidisciplinary cancer care teams, tumor board discussions, and as part of evaluations for clinical trials.

As thoracic oncology experiences a rapid growth of its disease treatment armamentarium, the regular use of palliative, supportive, and complementary therapies has become more vital. The shifting survival curve for thoracic malignancies has rendered engagement with patients to address physical, social, emotional, and spiritual issues only more pressing, including optimizing symptom control, emotional coping, and uncertainty management. Hence, together with forging novel treatments like immunotherapeutics, there should be a paralleled emphasis on patient-centered care, particularly around aligning care with patient goals, such as through advance care planning and goal setting, and improving patient QOL and satisfaction with care through the standard integration of palliative and supportive care services. Herein we review the evolving role of palliative and supportive care in an era of new therapies, the role of complementary therapies, and the value proposition for palliative and supportive care in the management of thoracic malignancies.

Evolving Role of Supportive Care in the Era of Novel Therapies and Prolonged Life Span

A growing body of evidence has emerged demonstrating improved patient-centered outcomes with the integration of palliative and supportive care into oncologic care. In light of this evidence, in 2012 ASCO prepared a provisional clinical opinion supporting the integration of palliative care into standard oncologic care. Given the growing strength and consistency of the evidence, ASCO more recently convened an expert panel in palliative care in oncology to perform a systematic review of this evidence and update of the 2012 provisional clinical opinion. The work resulted in the ASCO clinical practice guideline update published in 2017. The recommendations resulting from this practice guideline are summarized in Table 1.

This evidence is of particular importance to thoracic malignancies because the patient populations studied had...
TABLE 1. Summary of the 2017 ASCO Clinical Practice Guideline for Integration of Palliative Care Into Standard Oncology Care

<table>
<thead>
<tr>
<th>Specific Recommendation</th>
<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
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<tbody>
<tr>
<td>(1) Patients with advanced cancer should receive dedicated palliative care services, early in the disease course concurrent with active treatment</td>
<td>Evidence based: intermediate</td>
<td>Strong</td>
</tr>
<tr>
<td>(2) Palliative care services should be provided by interdisciplinary teams with consultation available in both the inpatient and outpatient settings</td>
<td>Evidence based: intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>(3) For newly diagnosed patients with an advanced cancer, early referrals to palliative care should occur, with the suggested timeframe being within 8 weeks of diagnosis</td>
<td>Evidence based: intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>(4) Among patients with cancer with high symptom burden and/or unmet physical or psychosocial needs, outpatient cancer care programs should provide and use palliative care services as a complement to their care</td>
<td>Evidence based: intermediate</td>
<td>Moderate</td>
</tr>
<tr>
<td>(5) For caregivers of patients with cancer, caregiver-tailored palliative care support should be considered, such as education or support offered remotely or in person</td>
<td>Evidence based: low</td>
<td>Weak</td>
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notable proportions of patients with lung cancer. A comprehensive overview of the research is provided in the ASCO clinical practice guideline; herein we will address two questions: (1) What is the evolving evidence informing expected outcomes when palliative care is concurrently provided to patient populations with lung cancer? (2) How can palliative and supportive care be integrated into the care of thoracic oncology patient populations?

What Is the Evolving Evidence Informing Expected Outcomes of Palliative Care in Patients With Lung Cancer?

In 2009, Bakitas et al. reported the findings of the ENABLE II (Educate, Nurture, Advise, Before Life Ends) randomized controlled trial (RCT) involving 312 patients with advanced cancer (35% had lung cancer) recruited from National Cancer Institute-designated rural cancer centers and Veterans Affairs-affiliated outreach clinics. A psychoeducational intervention was conducted by advanced practice nurses and consisted of four weekly educational sessions and monthly follow-up sessions. The primary outcomes were measures of QOL, including Functional Assessment of Therapy (FACT)-Palliative Care scale scores, symptom intensity, and resource use. The study showed that patients had improved QOL (p = .02), reduction in depressed mood (p = .02), and a trend toward lower symptom intensity (p = .06).

In 2010, Temel et al. reported findings of a single-institution RCT of early referrals to palliative care with standard oncology care versus standard oncology care alone among 151 patients with newly diagnosed metastatic non–small cell lung cancer (NSCLC). The primary endpoint was change in the score on the Trial Outcome Index from baseline to 12 weeks, which was composed of a sum of physical, functional well-being, and lung cancer subscales of the FACT-Lung scale. Patients in the early palliative care group were to receive a palliative care visit within 3 weeks of random assignment and at least once per month after the initial visit. Patients in the early palliative care group had better Trial Outcome Index scores (59 vs. 53; p = .009) and better FACT-Lung scores (98 vs. 91.5; p = .03) than the standard oncology care group at 12 weeks. Furthermore, there were also fewer depressive symptoms in the palliative care group versus the standard care group (6% vs. 38%, respectively; p = .01). Notably, despite fewer patients in the early palliative care group receiving aggressive end-of-life care (defined as chemotherapy within 14 days before death, no hospice care, or admission to hospice within 3 days of death) compared with the standard care group (33% vs. 54%, respectively; p = .05), median survival was longer among patients receiving palliative care (11.6 vs. 8.9 months; p = .02).

In 2014, Zimmermann et al. reported on a cluster RCT in which they compared early palliative care versus standard care among 461 patients with stage III or IV solid tumors with a poor prognosis (22% had lung cancer). Twenty-four medical oncology clinics were randomly assigned as to whether they would provide the palliative care intervention, which included palliative care consultation and monthly follow-up in the oncology palliative care clinic by a palliative care clinician and nurse. Telephone contacts were also provided, both at 1 week after the consultation and with a 24-hour call-in service for management of urgent issues. The primary outcome was change in QOL at 3 months as measured by the Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being. There was only a trend in improvement in the assessment score (p = .07), although there

PRACTICAL APPLICATIONS

- There is a compelling and growing body of evidence for routine integration of palliative care into lung cancer care with outcomes related to quality of life, depression, anxiety, health care utilization, and potentially survival.
- Palliative care integration into lung cancer care includes both foundational delivery of services from oncology teams and more specialized services from palliative care teams when needs dictate.
- There is a guiding framework from the American College of Chest Physicians for integration of complementary therapies into the care of patients with lung cancer.
- Palliative brings patient-centered and financial value to patients and oncology practices alike through six main, evidence-based drivers.
- Regular provision of palliative care services is a common theme found among high value oncology practices.
was significant improvement in secondary outcomes including the Quality of Life at the End of Life scale (p = .05) and in the measure of patient satisfaction with care (p = .003).

In 2015, Ferrell et al9 published findings of their quasi-experimental study of 491 patients with all stages of NSCLC, in which they compared usual care versus an interdisciplinary palliative care intervention. The usual care group was recruited first, followed by the intervention group. Patients in the intervention group received an initial nurse-completed comprehensive baseline assessment, including QOL, symptoms, and psychological distress, with presentation at an interdisciplinary meeting for creation of a personalized palliative care plan and recommendations for supportive care referrals. Patients in the intervention group also received four educational sessions organized around the physical, psychological, social, and spiritual domains of QOL. QOL endpoints were assessed at 12 weeks and included QOL and symptom burden (assessed by the FACT-Lung scale), spiritual well-being (assessed by the Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being scale), and psychological distress (as measured by the distress thermometer). Patients in the intervention group had better QOL (p < .001), improved symptoms (p < .001), greater spiritual well-being (p = .001), and lower psychological distress (p < .001) at 12 weeks, after controlling for baseline scores. Patients in the intervention group also had significantly higher numbers of completed advance care directives (44% vs. 9%; p < .001) and overall supportive care referrals (61% vs. 28%; p < .001). Notably, QOL benefits were seen largely in the patients with early-stage disease versus those with stage IV disease.

Finally, in 2017, Temel et al10 published results of their RCT of early palliative care among 350 patients with lung (55%) and gastrointestinal (45%) malignancies. The palliative care intervention was composed of visits with a palliative care clinician once a month until death, and those in the usual care group would receive palliative care upon request or referral. The primary study endpoint was change in QOL (FACT-General scale), and secondary endpoints included change in QOL from baseline to week 24, change in depression, and differences in end-of-life communication. This study found improvement in QOL at week 24 (p = .01) but not at week 12 (p = .39). Patients receiving the intervention had less depression at week 24 (p = .048) and also were more likely to discuss their care wishes with their oncologist if they were dying (30.2% vs. 13.5%; p = .004). Interestingly, the intervention effects varied by cancer type, with patients with lung cancer having improvements in measures of QOL and depression at weeks 12 and 24 (all p < .05).

These studies, as part of a larger body of evidence,4 point to the value of supportive care in lung cancer populations in improving patient outcomes. The bulk of these data are composed of patients with advanced lung cancers, although it is notable that the study by Ferrell et al9 included patients with all stages of lung cancer and the greatest benefits in outcomes were among those with earlier-stage disease. In summary, as reflected in the 2017 ASCO clinical guidelines,4 integration of palliative care into standard oncology care is supported by a body of evidence pointing to its beneficial impacts on QOL, symptom control, and psychosocial-spiritual well-being, together with improved end-of-life planning outcomes, for patients with lung cancer.

**How Can Palliative and Supportive Care Be Integrated into the Care of Patients With Lung Cancer?**

Based on the aforementioned research findings and guidelines, palliative care should be standardly integrated into the care of patients with advanced lung cancers at the time of initial diagnosis and approximately monthly thereafter. This presents a question regarding palliative care capacity, both because of the fact that outpatient palliative care resources are frequently limited and because patients with advanced lung cancer are living longer, yielding a greater population requiring care in palliative care clinics. Furthermore, although there is some evidence to support concurrent palliative care among patients with earlier-stage lung cancer,9 expanding to this population poses further need for palliative care resources to accommodate these patients.

In light of these practical challenges, three potential models for integrating palliative care into standard oncology care can be considered. All three models are based on an overarching generalist/specialist approach to palliative care delivery, as described by Quill and Abernathy11 and supported within the 2017 ASCO guidelines.6 In this model, basic management of symptoms, depression/anxiety, and patient/family communication regarding prognosis, goals of care, and advance care planning are expected roles and competencies on the part of the oncology clinical care team. In addition, all models assume inclusion of regular assessments of patient-reported outcomes metrics to ensure regular review of patient symptoms and other issues, with prompt interventions where needed. The use of patient-reported outcomes metric–based interventions in oncology is supported by a recent RCT by Basch et al,12 which demonstrated a survival benefit with their implementation.

Undergirded by generalist/specialist palliative care model and standard assessment of symptoms and other concerns via patient-reported outcomes metrics, potential models of integrated care delivery are as follows.

**Concurrent care model.** This model is most consistent with the evidence and is characterized by concurrent care—an initial consultation within 8 weeks of diagnosis followed by monthly patient visits—by an interdisciplinary palliative care team for all patients with advanced lung cancer and for patients with other disease stages who are identified through screening as having specialty palliative care needs. Although further research of appropriate triggers for specialty palliative care is required, the 2017 ASCO guidelines propose potential triggers based on extant evidence.6

**Triggered integration model.** This model is implemented when there are insufficient resources to meet outpatient palliative care needs required in the concurrent care model. In the triggered integration model, the oncology care team...
establishes dedicated resources within the oncology staff (e.g., an advance practice nurse) backed by interdisciplinary resources to provide concurrent palliative care within the oncology clinic. Key components of palliative care provided within the randomized trials have been summarized by the acronym TEAM. TEAM is characterized as follows. T represents time with the patient of at least 1 extra hour per month at regular intervals dedicated to palliative care issues. E denotes education and includes ongoing, structured discussions about managing symptoms, goals, preferences for care, prognostic understanding, advanced care planning, and communication of these discussions with the health care team. A represents assessments that systematically (e.g., electronically available patient-reported outcomes metrics) query patients about symptoms (e.g., Edmonton Symptom Assessment System), psychosocial well-being (e.g., Patient Health Questionnaire-2), spirituality (e.g., the FICA Spiritual Assessment Tool, which assesses faith and belief, importance, community, and areas to address in care11), distress (e.g., distress thermometer), and caregiver issues. Finally, M refers to management and includes referrals to interdisciplinary services that are triggered when assessments identify specific palliative care needs. Established protocols should provide clear pathways for when to involve interdisciplinary services (e.g., psychosocial needs resulting in a mental health provider referral).

**Concurrent and triggered integration model.** A third potential model is a hybrid of the aforementioned models, in which palliative care services are concurrently provided to all patients with advanced cancer but in addition, there is a dedicated generalist palliative care provider integrated into the oncology clinic. This provider regularly assesses patients receiving palliative care services who, as high-risk patients, may have issues arise between their palliative care visits and provides ongoing assessments of all patients with lung cancer who may not be receiving palliative care services. This service can expeditiously identify palliative care issues for immediate intervention and/or for specialty referrals. This third model may also function well where outpatient palliative care services are present but may be insufficient in capacity to provide all ongoing palliative care follow-up.

In summary, there is strong evidence to support concurrent palliative care services in the care of patients with advanced lung cancer. This added layer of support should also be considered for patients of earlier-stage lung cancers, particularly where assessments indicate palliative care needs. Models of palliative care delivery should be established in oncology clinics, with the concurrent care model being most consistent with the evidence. In light of insufficient palliative care resources to meet the needs of a growing population of patients living with advanced lung cancers, adaptations such as the triggered integration model and the hybrid concurrent/triggered model can also be considered.

**VALUE AND COST OF PALLIATIVE AND SUPPORTIVE CARE**

Over the last decade, the evidence base supporting improvement in patient and caregiver outcomes through routine integration of palliative care into oncology care has transitioned from nascent to robust. In response, palliative care consultation teams across the United States have grown by leaps and bounds, with a more than threefold increase in availability in less than 2 decades. Paralleling the growth of palliative care, oncologists have experienced wholesale changes in how cancer care is delivered, including an imperative to demonstrate robust links between services rendered and value. This shift toward pay-for-value has led to thoughtful searches across the field to maximize the delivery of high-value services while root out and reducing those services that do not improve outcomes of importance.

**The Value Imperative for Palliative Care**

A consistent characteristic of high-value oncology care is regular and normalized delivery of palliative care. This has been observed in both qualitative reviews of high-value practices alongside large prospective studies. For example, Blayney et al18 studied seven high-value practices, finding a common theme among them related to early and routine palliative care integrated into usual oncology care. Furthermore, they found regular deployment of care practices that focus on goal setting and supporting the patient journey through cancer, indicating a culture that embraces the delivery of palliative care philosophies both by the oncology team and palliative care specialists. In fact, the expert oncologist panel judged routine integration of palliative care as one of the top three attributes to carry the highest immediate potential for lowering spending without compromising the quality of care. Additionally, we performed our own analyses of preferred care practices that meet quality measures in reimbursement arrangements that stress high value, such as the oncology care model. To no surprise, there can be clear relationships drawn between most quality measures in the oncology care model and proven ways palliative care can improve those measures.

Yet the value proposition for palliative care integration into oncology care also requires quantitative, prospectively collected data with real-world implementation. The “value proposition,” a term often used in the business world to denote the differentiating value brought on by a new product or service, of palliative care integration centers around two key arguments. First, palliative care increases indirect sources of revenue for health care organizations. Second, palliative care maximizes cost savings related to decreased provisions of low-value care. The former can include bonuses and payments related to improvements in patient satisfaction and hospital readmission scores, whereas the latter is achieved through lesser delivery of unreimbursed care (e.g., that exceeds the allotted Disease-Related Group code), and low-value care near the end of life (e.g., chemotherapy in the last days, transfers to intensive care units with no goals). Importantly, the value proposition is not rooted in the increasingly outdated fee-for-service model; specialty palliative care services are generally cost centers, not contribution margin drivers.
Moving along the accounting ledger, in addition to building assets associated with cost savings to patients, clinical organizations, and payers, palliative care naturally has costs of its own. Because of their multidisciplinary nature, services can be associated with high fixed costs related to clinician salaries. Furthermore, with the bimodal age and experience distribution in the specialty palliative care workforce and with many clinicians entering the field as a second career,20 clinician salaries can be high. Additionally, because many programs are starting from scratch, recruitment, onboarding, and administrative costs related to necessary startup activities are often substantial. Thus, the value proposition is truly a balance between the direct costs related to starting and running a team, the indirect costs (e.g., opportunity costs when resources are taken away from other areas to support palliative care), and the potential value realized by patients, caregivers, health systems, and payers.

**A Building and Compelling Evidence Base for Palliative Care Maximizing Value**

To address all components of the value proposition argument for greater palliative care integration, outcomes important to patients, health systems, and payers have been seamlessly weaved into study designs from even the earliest of studies. For example, one of the earliest home-based palliative care trials 15 years ago by Brumley et al21 demonstrated among 500 patients in an integrated health system profound benefits from the “extra layer of support” that palliative care adds. These benefits included increased satisfaction with services at 60 days after enrollment and significantly fewer emergency department visits, hospital days, skilled nursing facility days, and physician visits than those in the comparison group. Those enrolled in palliative care averaged a 45% decrease in costs compared with patients that received usual care. In 2011, Morrison et al22 first demonstrated sizable fixed and variable costs savings for hospitalized patients evaluated by palliative care. They showed that there was an adjusted net savings of $1,696 in direct costs per admission and $279 in direct costs per day for palliative care patients who were discharged alive compared with controls. Greater costs savings were seen among those patients who died during the inpatient admission; there was an adjusted net savings of $4,908 in direct costs per admission and $374 in direct costs per day, including substantial reductions in intensive care unit costs, for palliative care patients who died compared with controls. Similar analyses demonstrated cost savings up to $6,900 for Medicaid patients, including reductions of $4,098 in hospital costs per admission for patients discharged alive and $7,563 for patients who died in the hospital. Demonstrating dramatic cost reductions when considering palliative care as a population health strategy, the authors estimated that the reductions in Medicaid hospital spending in New York State alone could be as high as $252 million annually.23

As patient and caregiver outcomes from prospective trials started to emerge, outcomes related to value and health care utilization were reported. For example, the aforementioned RCT by Temel et al,4 demonstrating a potential survival benefit with palliative care compared with usual care, also reported no cost increases with the addition of palliative and hospice services while also demonstrating lower chemotherapy-related costs.24,25 This is remarkable, considering that patients did not overall receive less chemotherapy in the palliative care intervention arm, just less near the end of life. Further reviews of studies have continued to confirm the concept of predictable cost savings associated with palliative care integration, across both outpatient and inpatient delivery.26,27 Table 2 summarizes key studies that demonstrate outcomes related to health care value improved by palliative care integration into oncology.

**The Road Ahead: Value and Palliative Care Hand in Hand**

Oncology will always remain one of the most resource-intensive medical disciplines. Caring for those with substantial morbidity, using methods that are often costly because of their cutting-edge characteristics, while using a multidisciplinary team to address needs from all angles comes at a cost. Yet we are learning that routine integration of palliative care into oncology care can curb costs that are unnecessary and can prevent health care utilization that is not wanted, all while supporting patient preferences and values. This counters any myth that cost savings as a result of palliative care involvement originate from anything other than supporting patient wishes. It turns out that doing the right thing, as defined by patients and their caregivers, leads to appropriate resource utilization when warranted and savings for all when not.

**INTEGRATIVE HEALTH APPROACHES IN THE CARE OF PATIENTS WITH LUNG CANCER**

Having explored evidence undergirding the integration of palliative care services into the care of patients with lung cancer, including its evidence-based role in care and resultant value associated with integration, we now turn to examining the role of integrative oncology in the care of patients with lung cancer. Integrative oncology is now recognized as a supportive and adjunctive model of care for patients with lung cancer; in 2013, the American College of Chest Physicians published evidence-based practice guidelines to facilitate implementation of integrative health approaches in lung cancer care.34,35

Recently, a consensus group defined integrative oncology as “a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments. Integrative oncology aims to optimize health, quality of life, and clinical outcomes across the cancer care continuum and to empower people to prevent cancer and become active participants before, during, and beyond cancer treatment.”35

The core purpose of integrative oncology converges with a holistic, biosocial, personalized approach to the patient and moves away from the reductionist model of disease.
described by Greene and Loscalzo.\textsuperscript{36} Integrative oncology serves to “put the patient back together” by introducing evidence-based complementary therapies to address the physical, emotional, and spiritual impact from cancer and its sequelae.

Complementary therapies are increasingly supported by the literature to address many of the unique problems faced by the patient with lung cancer. With lung cancer as the leading cause of cancer death, it is not surprising that patients often experience a high burden of symptoms, poorer prognoses, and social stigmatization related to their smoking history. Taken together, these factors, in addition to the complexities related to treatment, all lead to increased psychosocial and physical distress.\textsuperscript{37}

In Table 3, we have summarized the 2013 American College of Chest Physicians evidence-based practice guidelines for complementary therapies in integrative medicine and lung cancer.\textsuperscript{34} In this section, we have also included some updated evidence since its publication.

In these guidelines, the authors note that the commonly used term CAM (complementary and alternative medicine) is often used to describe adjunctive therapies and includes both complementary strategies, which are evidence-based, and alternative therapies, which are largely unproven methods. The guidelines review only complementary modalities and are based on a large systematic literature review of meta-analyses, systematic reviews, RCTs, and prospective cohort studies in accordance with the American College of Chest Physicians evidence-based clinical practice guidelines development methodology. Because patients with lung cancer experience symptoms such as anxiety, nausea, vomiting, and pain, which are associated with treatment of all patients with cancer, another guideline (“2017 Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment”) may provide additional guidance in the use of complementary therapies for patients with lung cancer.\textsuperscript{38}

Some of the common modalities used in lung cancer treatment with reasonable evidence include mind-body modalities, massage, exercise, acupuncture, and nutrition. In China, Chinese herbal medicines are used extensively in the different stages of the patient’s cancer journey. However, in the West, Chinese herbal medicine is rarely studied adequately to provide sufficient evidence to guide its use for patients with cancer. Practice guidelines have been developed by Chinese oncology experts to enhance the efficacy of targeted treatments, prolong survival, decrease treatment side effects, and improve QOL. These guidelines are based on several decades of research ranging from case series to RCTs and are of varying quality.\textsuperscript{39-44} For example, Chinese herbal medicines demonstrated beneficial effects when used concomitantly with icotinib by patients with advanced NSCLC in a recent study.\textsuperscript{41}

**Table 2. How Palliative Care Promotes Value**

<table>
<thead>
<tr>
<th>Value Driver</th>
<th>Mechanism of Palliative Care Action</th>
<th>References*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater patient satisfaction</td>
<td>Facilitation of shared decision-making conversations, focus on values and preferences of patients and caregivers</td>
<td>El-Jawahri et al, Zimmermann et al, Rabow et al</td>
</tr>
<tr>
<td>Lower hospital admission costs</td>
<td>Early and frequent goals of care conversations, reduced length of stay</td>
<td>Morrison et al, May et al</td>
</tr>
<tr>
<td>Decrease in hospital readmissions</td>
<td>Timely and comprehensive symptom management, early goals of care conversations, increased referrals to hospice</td>
<td>Adelson et al, Enguidanos et al, O’Connor et al</td>
</tr>
<tr>
<td>Less costs from chemotherapy</td>
<td>Less prescribing of chemotherapy in the final days of life</td>
<td>Greer et al</td>
</tr>
<tr>
<td>High adherence to end-of-life quality measures</td>
<td>Focus on higher value care near the end of life</td>
<td>Ziegler et al</td>
</tr>
<tr>
<td>Decrease in emergency department visits and hospital days</td>
<td>Timely assessment of distress and offering of nonacute care services to address needs</td>
<td>Brumley et al, Lustbader et al</td>
</tr>
</tbody>
</table>

*Representative references, not exhaustive.

Mind-Body Modalities

Mind-body modalities refer to healing techniques administered by professionals that enhance health by focusing on brain, mind, body, and behavioral interactions, as well as the impact of emotional, mental, social, spiritual, experiential, and behavioral factors on overall well-being.\textsuperscript{41-44} Deng et al specifically addressed the modalities of yoga, tai chi/qigong, hypnosis, music therapy, psychosocial/relaxation techniques, as well as mediation and mindfulness-based stress reduction. The first three modalities (tai chi, qigong, and yoga) all involve integration of breathing, meditation, and aerobic movements. In traditional Chinese medicine, tai chi and qigong are used to balance the vital life energy (qi), resulting in improved immune and cardiovascular function and stress reduction. A small study of 32 patients with NSCLC who had undergone a thoracotomy showed no increase in cortisol level in the tai chi group compared with...
the control group. Another meta-analysis of 13 trials and 592 subjects found that qigong/tai chi positively affected QOL, fatigue, immune function, and cortisol levels of patients with cancer. The authors noted that there was a high risk of bias included in the trials and that further, more rigorous studies are needed. Well-controlled trials have confirmed that yoga may improve mood, stress, QOL, and sleep, as well as chemotherapy-induced nausea/anticipatory nausea, pain, fatigue, and appetite.

### Psychosocial Interventions

Deng et al evaluated six systematic reviews and one meta-analysis involving 178 studies and more than 20,000 patients with lung cancer. The authors were not able to demonstrate a survival benefit for psychosocial interventions, but they determined that (1) cognitive-behavioral therapy was beneficial in improving QOL, depression, anxiety, pain, fatigue, and distress; (2) behavioral methods reduced nausea, vomiting, anticipatory nausea and vomiting, anxiety, and depression; and (3) relaxation training ameliorated tension, anxiety, mood and hostility, while reducing blood pressure/heart rate, nausea, sleep disturbance, and pain. A more recent review by Lehto et al looked at psychosocial interventions in lung cancer therapies, including cognitive-behavioral therapies, psychoeducation, mind-body exercise, and supportive/palliative care strategies. Further well-designed studies are needed to provide additional guidance in using these therapies.

### Acupuncture

Acupuncture has been used clinically in traditional Chinese medicine for more than 2,500 years. A recent article from the National Cancer Institute conference on acupuncture for symptom management in oncology reviewed the state of the science, evidence, and research gaps. Some mechanistic studies show that acupuncture point stimulation has modulatory effects on the central and peripheral nervous systems, including the autonomic nervous system. Deep tissue sensory afferent nerves are stimulated and activate central nervous system pathways that control sensory modulation and autonomic regulation. Prolonged stimulation

### TABLE 3. Complementary Therapies in Lung Cancer as Part of a Suggested Multidisciplinary Approach

<table>
<thead>
<tr>
<th>Approach</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initiation of complementary therapies</strong></td>
<td></td>
</tr>
<tr>
<td>Ask all patients with lung cancer about their interest in using complementary therapies, and counsel on risks and benefits</td>
<td>2C</td>
</tr>
<tr>
<td><strong>Mind-body modalities interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Use mind-body modalities to reduce anxiety, mood disturbance, and sleep disturbance in symptomatic patients and to improve QOL</td>
<td>2B</td>
</tr>
<tr>
<td>Use mind-body modalities to reduce acute or chronic pain in symptomatic patients</td>
<td>2B</td>
</tr>
<tr>
<td>Use mind-body modalities to reduce anticipatory chemotherapy-induced nausea and vomiting</td>
<td>2B</td>
</tr>
<tr>
<td>Use yoga (a movement-based mind-body modality) to reduce fatigue and sleep disturbance and improve mood and QOL in symptomatic patients</td>
<td>2B</td>
</tr>
<tr>
<td><strong>Massage</strong></td>
<td></td>
</tr>
<tr>
<td>Add massage therapy by trained professionals for anxiety and pain, not adequately controlled by usual care</td>
<td>2B</td>
</tr>
<tr>
<td><strong>Exercise-based pulmonary rehabilitation interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Provide supervised exercise-based pulmonary rehabilitation to improve cardiorespiratory fitness and functional capacity in patients with compromised lung function awaiting pulmonary resection for suspected lung cancer</td>
<td>2C</td>
</tr>
<tr>
<td>Provide supervised exercise-based pulmonary rehabilitation to improve postsurgical cardiorespiratory fitness and functional capacity in patients with lung cancer</td>
<td>2C</td>
</tr>
<tr>
<td>Provide supervised exercise-based pulmonary rehabilitation to improve cardiorespiratory fitness and functional capacity in patients with lung cancer with compromised lung function receiving palliative anticancer therapy</td>
<td>2C</td>
</tr>
<tr>
<td><strong>Acupuncture</strong></td>
<td></td>
</tr>
<tr>
<td>Use acupuncture for patients with chemotherapy or radiation-associated nausea or vomiting</td>
<td>2B</td>
</tr>
<tr>
<td>Use acupuncture for patients with inadequately controlled cancer-related pain and peripheral neuropathy</td>
<td>2C</td>
</tr>
<tr>
<td><strong>Diet interventions</strong></td>
<td></td>
</tr>
<tr>
<td>Recommend a diet rich in nonstarchy vegetables and fruits to reduce the risk of cancer in patients who may develop lung cancer</td>
<td>2C</td>
</tr>
<tr>
<td>Limit consumption of a large amount of red meat and processed meat in patients who may develop lung cancer, because lower red meat intake may reduce the risk of lung cancer</td>
<td>2C</td>
</tr>
<tr>
<td>Add high-calorie and high-protein supplements (1.5 kcal/mL) to the diets of patients with weight loss undergoing treatment of lung cancer to achieve weight stabilization</td>
<td>2C</td>
</tr>
<tr>
<td>Use oral supplementation with n-3 fatty acids to improve nutritional status in patients with sarcopenia</td>
<td>2C</td>
</tr>
</tbody>
</table>

Abbreviation: QOL, quality of life.
activates brainstem descending diffuse noxious inhibitory pathways to produce analgesia. Furthermore, functional MRI studies demonstrate that acupuncture influences the activity of the insula and limbic system related to affective responses and pain modulation, as well as the activity of somatosensory areas S1 and S2. There is also evidence of peripheral nerve sensory modulation mediated by adenosine. Finally, some of the long-term effects of acupuncture may be explained by cortical plasticity and effects on opioid binding. Given the substantial unmet symptom management needs and accumulating research evidence, use of acupuncture is recommended for pain, cancer-related fatigue, chemotherapy-related nausea and vomiting, likely xerostomia, as well as palliative care and cancer survivorship.⁴⁷

**Massage Therapy**

Massage therapy uses the hands or mechanical devices to manipulate the muscles and reduce muscle tension and pain. In a small meta-analysis, Lee et al⁴⁸ found that massage therapy compared with no massage or conventional care significantly reduced short-term cancer pain. However, the study was limited by inclusion of RCTs and case-controlled trials with possible selection bias.⁴⁹ Deng et al³⁴ concluded that there is moderate-strength evidence from RCTs that supports the use of massage to decrease anxiety and pain for patients with cancer.

**Nutrition**

Nutritional care appears to be beneficial in all phases of lung cancer from prevention to treatment to survivorship. Evidence suggests a decreased risk of lung cancer with increased intake of fruits and nonstarchy vegetables, cruciferous vegetables, and carotenoid intake from foods (not supplements). Notably, some data show an inverse correlation between vegetable consumption and lung cancer incidence in smokers. During lung cancer treatment, calorie- and protein-dense supplementation is suggested based on studies of other patients with cancer with weight loss, anorexia, and cachexia. Finally, patients with cancer and sarcopenia have depleted omega-3 fatty acids, and preliminary results from RCTs of patients with NSCLC with sarcopenia demonstrate that the benefits of omega-3 fatty acid supplementation (known for its anticachetic effects), both during and after treatment, outweigh the risks.³⁴

**Exercise**

Finally, supervised exercise-based pulmonary rehabilitation was suggested in the 2013 American College of Chest Physicians guidelines,³⁴ not only for patients with suspected lung cancer awaiting pulmonary resection but also for patients with postoperative and inoperable lung cancer. The recommendations are based on a few studies that demonstrate notable improvement in cardiovascular fitness and functional capacity before surgery and modest improvement in exercise capacity and QOL after surgery. For patients with inoperable disease, there are preliminary data showing modest improvements in exercise tolerance and functional capacity among patients able to follow the regimen. RCTs are needed to increase the strength of this recommendation.

**Clinical Considerations**

By establishing the evidence-based guidelines that we have reviewed, the American College of Chest Physicians has provided a framework for clinicians and health systems to disseminate and implement complementary methods (mind-body modalities, massage, exercise, acupuncture, and nutrition) in the care of the patient with lung cancer.

Based on our center’s experience at the University of California, Los Angeles, for close to 25 years, we have developed a person-centered, healing-oriented model to help patients with serious refractory problems, including those at various stages of their cancer journey. Using an integrative oncological approach, we help patients manage their stress at the time of their diagnosis, support them through the rigor of treatment to minimize both short- and long-term side effects, and work with them to maintain remission or to slow the progression of disease. This model emphasizes palliation at all stages of the disease process, focusing on enhancing QOL. Additional clinical considerations include the following: (1) the patient and his or her family’s right to select a treatment plan based on individual values, beliefs, and available evidence; (2) access to resources, including accessibility to and availability of competent providers; and (3) insurance coverage. The hope is that integrative health/palliative care, appropriate for people at any age and any stage of a serious illness, would become more available to address the clinical, emotional, psychosocial, and spiritual concerns of the patient and family—a biopsychosocial-ecological-spiritual model of care.⁴⁹ ⁵¹

**CONCLUSION**

Supportive care has experienced remarkable growth and acceptance in oncology care, particularly as the evidence base has grown, demonstrating improvements in notable patient outcomes associated with these services. In light of that body of evidence, the standard integration of palliative and supportive care services is now recommended for all patients with advanced cancer. This body of evidence has particular relevance to lung cancer, as many of the populations studied included, or solely represented, patients with lung cancer. The value of the standard integration of supportive care services has also been well demonstrated, further underscoring the rationale for integration. Finally, the evidence base supporting the inclusion of an integrative health care approach within supportive care services is also growing, and guidelines highlight how integrative modalities serve as part of a holistic approach to the care of patients with lung cancer. The modern era of lung cancer therapies includes an integrated emphasis on patient-centered care through the standard integration of supportive care services to improve value and patient well-being throughout the cancer care continuum, from diagnosis to survivorship or end-of-life care.
References


Sequencing Therapy for Genetically Defined Subgroups of Non–Small Cell Lung Cancer

Helena A. Yu, MD, David Planchard, MD, PhD, and Christine M. Lovly, MD, PhD

OVERVIEW

The practice of precision medicine for patients with metastatic non–small cell lung cancer (NSCLC), particularly those patients with adenocarcinoma histology (the predominant subtype of NSCLC), has become the accepted standard of care worldwide. Implementation of prospective tumor molecular profiling and rational therapeutic decision-making based on the presence of recurrently detected oncogenic “driver” alterations in the tumor genome has revolutionized the way that lung cancer is diagnosed and treated in the clinic. Over the past two decades, there has been a deluge of therapeutically actionable driver alterations and accompanying small molecule inhibitors to target these drivers. Herein, we synthesize a large and rapidly growing body of literature regarding therapeutic inhibition of driver mutations. We focus on established targets, including EGFR, anaplastic lymphoma kinase (ALK), ROS1, BRAF, RET, MET, HER2, and neurotrophic tyrosine kinase receptor (NTRK), with a particular emphasis on the sequencing of small molecule inhibitors in these genetically defined cohorts of patients with lung cancer.

SEQUENCING AGENTS IN THE TREATMENT OF PATIENTS WITH EGFR-MUTANT LUNG CANCER

**EGFR**-mutant lung cancers represent 12% to 17% of all lung adenocarcinomas. EGFR mutations—most commonly small deletions in exon 19 (19del) or point mutations in exon 21 (L858R)—identify a subset of patients who are most appropriately treated with first-line EGFR TKIs. Many prospective studies have compared first-line EGFR TKIs with standard cytotoxic platinum doublet chemotherapy and have confirmed the superior response rates and progression-free survival with EGFR TKIs compared with chemotherapy in patients with **EGFR**-mutant lung cancers. First-generation (erlotinib, gefitinib) and second-generation (afatinib) EGFR TKIs have multiple global approvals for first-line treatment of patients with metastatic **EGFR**-mutant lung cancers (Table 1). Dacomitinib (a second-generation EGFR TKI) has recently been compared head to head with gefitinib, revealing an increase in median progression-free survival (mPFS; 14.7 vs. 9.2 months, respectively). The results on overall survival are expected this year and could lead to a new regulatory approval.

**Established Treatments**

These first- and second-generation EGFR TKIs are effective therapies, but the majority of patients develop disease progression on these agents after 8 to 10 months. It has become standard of care to rebiopsy patients at the time of clinical progression, and the acquired molecular alterations identified serve as the molecular mechanisms of resistance to EGFR TKI treatment. Another emerging option is liquid biopsy where tumor cfDNA within plasma is utilized for mutation testing. This has emerged as a viable alternative to tumor rebiopsy. The most common acquired mutation is **EGFR** T790M, but other acquired alterations include **MET** amplification, **HER2** amplification, **PIK3CA** mutations, small cell histologic transformation, and epithelial to mesenchymal transition. To address these resistance mechanisms to EGFR TKIs, multiple combination treatments using first- and second-generation EGFR TKIs have been assessed. EGFR TKIs have been combined with EGFR antibodies, mTOR inhibitors, HDAC inhibitors, HSP90 inhibitors, MET inhibitors, dasatinib, cabozantinib, and other agents with limited efficacy seen with the combinations.

**Osimertinib**

Osimertinib is a third-generation, mutant-selective, covalent EGFR inhibitor (Table 1) that targets both the sensitizing **EGFR** mutations as well as **EGFR** T790M. Its initial approval in many countries is for patients with **EGFR**-mutant lung cancers who were previously treated with an EGFR TKI and have acquired EGFR T790M. This approval was based on the phase I AURA study and confirmed by a randomized study of osimertinib versus platinum doublet chemotherapy.
in this clinical setting. Patients treated with osimertinib as second-line EGFR TKI had an overall response rate (ORR) of 71% and an mPFS of 10.1 months. Based on the efficacy in the later-line setting, osimertinib was subsequently assessed prospectively in a randomized phase III study of osimertinib or standard of care EGFR TKI (erlotinib or gefitinib) as first-line treatment of patients with metastatic lung adenocarcinoma in the FLAURA study. In the first-line setting, the mPFS on osimertinib was 18.9 months compared with 10.2 months with standard EGFR TKIs. Based on these data, osimertinib is expected to receive global approval as a first-line treatment option for patients with metastatic EGFR-mutant lung cancers.

Resistance to Osimertinib and New Combination Therapies
Patients treated with osimertinib also develop resistance attributable to acquired molecular alterations. There are less robust data to suggest which mechanisms of resistance occur frequently and are clinically meaningful, and we do not yet have any data on mechanisms of resistance to first-line treatment with osimertinib. Resistance mechanisms identified to third-generation EGFR TKIs include acquired EGFR C797T mutation (C797 is the site at which osimertinib binds to the EGFR kinase domain), 20,21 loss of EGFR T790M, 22 MET and HER2 amplification, 23,24 YES1 amplification, 25,26 and acquired mutations, including KRAS, PIK3CA, and HER2.24,27

New combinations will presumably be assessed both in the first-line setting and after progression on osimertinib to attempt to prevent and reverse resistance to osimertinib, respectively. The combination of osimertinib and savolitinib, an MET inhibitor, has shown activity in patients with MET amplification after EGFR TKI therapy with erlotinib, afatinib, gefitinib, or osimertinib. Other combinations that are being assessed include osimertinib and bevacizumab (NCT02803203, NCT03133546, and NCT02971501), osimertinib and selumetinib (NCT03392246), osimertinib and dasatinib (NCT02954523), osimertinib and the JAK inhibitor INCBO39110 (NCT02917993), osimertinib and navitoclax (NCT02520778), and osimertinib and an mTOR inhibitor MLN0128 (NCT02503722) among others. With the milder toxicity profile of osimertinib compared with earlier-generation EGFR inhibitors, combination studies may prove to be more efficacious by reaching optimal doses of both drugs before being limited by toxicity.

Sequencing of EGFR Inhibitors
As a general practice, our most effective treatments should be used first, because there is a clear minority of patients who progress quickly with declining functional status and do not receive second-line therapy—as high as 50% in historical data sets. Other factors that should be considered when choosing a first-line treatment of this population include toxicity profile and central nervous system (CNS) efficacy. In the FLAURA study, there were fewer patients with greater than or equal to grade 3 toxicities, fewer fatal adverse events, and a lower rate of adverse events leading to permanent discontinuation with osimertinib compared with standard EGFR TKI. In addition, there were fewer events of CNS progression with osimertinib compared with standard EGFR TKI (6% vs. 15%). Osimertinib is well positioned to be the new first-line treatment of choice because of a marked improvement in efficacy and superior CNS penetration/efficacy while also being better tolerated by patients.

One potential criticism of first-line osimertinib is that there are no approved EGFR-directed treatments after progression on osimertinib. However, only 50% of patients on standard EGFR TKI acquire EGFR T790M and are eligible for second-line osimertinib, and the additive time on treatment with a standard EGFR TKI followed by osimertinib is essentially equivalent to the time on first-line osimertinib. After clinical progression on first-line osimertinib in the setting of C797S and the absence of EGFR T790M, there are preclinical data to suggest efficacy of a standard EGFR TKI, such as gefitinib, in that setting. We await clinical data that such sequencing is a viable option.
# TABLE 1. Targeted Therapies Currently Approved and Under Development for Lung Cancer

<table>
<thead>
<tr>
<th>Mutation and Drug</th>
<th>Category/Description</th>
<th>Approval Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR mutations</strong></td>
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<td>Nazartinib (EGF816)</td>
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<td>Crizotinib (PF2341066)</td>
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<td>Lorlatinib</td>
<td>ROS1, ALK, multikinase inhibitor</td>
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<td>Cabozantinib</td>
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</table>
SEQUENCING TARGETED AGENTS

Other Strategies to Improve Outcomes for Patients With EGFR-Mutant Lung Cancers

There is substantial heterogeneity in the clinical course of patients with EGFR-mutant lung cancers. As next-generation sequencing of tumors becomes the standard of clinical care, we will be able to discern the impact of concurrent genetic alterations in addition to activating EGFR mutations within lung cancers. Several reports have shown concurrent TP53 alterations to be a negative prognostic factor associated with shorter overall survival. In addition, several pretreatment concurrent alterations, including HER2 amplification, MET amplification, and TP53 mutations, seem to be associated with shorter time to progression on EGFR TKIs. Highlighting concurrent alterations that may have prognostic significance is important, because it identifies a subset of patients with poorer outcomes on whom new therapeutic options should be focused.

Data from the ASPIRATION study and others have shown the utility of treatment with EGFR TKIs beyond radiographic progression in the setting of more indolent disease and in the absence of symptoms. Treatment beyond progression allows for additional clinical benefit and delays the time before new treatments are required. Cancers can be heterogeneous in their response and resistance to therapy, such as a scenario where the majority of the target lesions continue to respond to treatment while one lesion has begun to grow. In this situation, local therapy to the oligoprogressive metastasis followed by continuing previous systemic therapy is another means to prolong time on treatment that is largely continuing to benefit a patient.

SEQUENCING AGENTS IN THE TREATMENT OF PATIENTS WITH ALK-REARRANGED LUNG CANCER

ALK-Rearranged Lung Cancer

Rearrangements in the gene encoding the ALK on chromosome 2p were first discovered as oncogenic driver alterations in NSCLC in 2007. These chromosomal rearrangements result in the production of a chimeric fusion protein—most commonly EML4-ALK, although several other ALK fusions have been described. ALK rearrangements are detected in approximately 4% to 8% of NSCLCs and can be detected in tumor samples by several diagnostic measures, including immunohistochemistry, fluorescence in situ hybridization, and next-generation sequencing.

Overview of ALK TKIs in Clinical Use

Now, approximately 10 years after the initial discovery of ALK as a lung cancer driver, there have already been numerous large, international, prospective clinical trials testing the efficacy of ALK TKIs in this patient population. Remarkably, five ALK TKIs have already gained regulatory approval (Table 1). These ALK TKIs can be broken down into three “generations” of inhibitors defined by increasing “on-target” efficacy toward ALK. Crizotinib was the first ALK TKI developed in the clinic and the first ALK TKI to obtain regulatory approval. Crizotinib also targets MET and ROS1 (described below). Therefore, the development of more potent and more specific second- and third-generation inhibitors was needed (Table 1). Below, we summarize a large amount of clinical trial data discussing the sequencing of ALK TKI therapies.

<table>
<thead>
<tr>
<th>Mutation and Drug</th>
<th>Category/Description</th>
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<td><strong>MET exon 14 skipping mutation</strong></td>
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<td>Capmatinib</td>
<td>MET selective inhibitor</td>
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TABLE 1. Targeted Therapies Currently Approved and Under Development for Lung Cancer (Cont’d)
**First-line Therapy for ALK-Rearranged Lung Cancer**

Crizotinib was the first ALK TKI to be approved for first-line treatment of ALK+ lung cancer based on the PROFILE 1014 study.\(^{38}\) This phase III trial enrolled 343 patients who were treatment naïve and randomized them to crizotinib or chemotherapy (platinum/pemetrexed). Cross over to crizotinib treatment after disease progression was permitted for patients receiving chemotherapy. The ORR was 74%, mPFS was 10.9 months, and hazard ratio (HR) for progression or death in the crizotinib group was 0.45 (95% CI, 0.35–0.60). Crizotinib is approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency for first-line therapy of ALK+ NSCLC.

More recently, ceritinib, a second-generation ALK TKI, has also been approved for first-line treatment of ALK+ lung cancer based on the ASCEND-4 study.\(^{39}\) This study enrolled patients with metastatic ALK+ NSCLC who were treatment naïve and had asymptomatic, neurologically stable brain metastases; 189 patients were randomly selected to receive ceritinib (750 mg orally once a day), and 187 patients were randomly selected to receive platinum/pemetrexed for four cycles (maintenance pemetrexed was allowed). Crossover to ceritinib was permitted after disease progression for patients receiving chemotherapy. mPFS was 16.6 months (95% CI, 12.6–27.2) in the ceritinib group and 8.1 months (95% CI, 5.8–11.1) in the chemotherapy group (HR 0.55; 95% CI, 0.42–0.73; \(p < .00001\)).

In patients with measurable CNS lesions at baseline, the confirmed overall intracranial response rate was 57% (95% CI, 37%–76%) in the ceritinib arm and 22% (95% CI, 9%–42%) in the chemotherapy arm. The most common adverse events in the ceritinib arm were diarrhea (85% all grades, 5% grade 3/4), nausea (69% all grades, 3% grade 3/4), vomiting (66% all grades, 5% grade 3/4), and an increase in liver function enzymes. The ASCEND-8 trial\(^{40}\) evaluated a lower dose of ceritinib (450 mg) in patients and found it to be similarly efficacious; the mPFS in the 450-mg dose arm was 17.6 months compared with 10.9 months in the 750-mg dose arm. There were also improvements with the 450- versus 750-mg dose arm for grade 3/4 diarrhea (1.1% vs. 7.8%), nausea (0% vs. 5.6%), and vomiting (0% vs. 4.4%).

Alectinib, another second-generation ALK TKI, has also been tested in the first-line setting. In the global phase III ALEX study, 286 patients with advanced/metastatic ALK+ NSCLC who were treatment naïve were enrolled and randomized to receive alectinib (600 mg orally twice a day; 152 patients) or crizotinib (250 mg orally twice a day; 151 patients).\(^{41}\) Platinum-based chemotherapy was not the comparator in the ALEX study. Asymptomatic brain metastases were allowed. mPFS (investigator assessment) was not reached (17.7 months to not reached) for alectinib and 11.1 months (9.1–13.1) for crizotinib, with an HR of 0.47 (95% CI, 0.34–0.65; \(p < .0001\)). For patients with baseline CNS metastases, mPFS was not reached (9.2 months to not reached) for alectinib and 7.4 months (6.6–9.6) for crizotinib, with an HR of 0.40 (95% CI, 0.25–0.64). For patients without baseline CNS metastases, mPFS was not reached for alectinib and 14.8 months (10.8–20.3) for crizotinib, with an HR of 0.51 (95% CI, 0.33–0.80). Compared with the crizotinib arm, patients in the alectinib arm experienced more myalgias (16% all grades), weight gain (10% all grades), and laboratory abnormalities, including elevated bilirubin (15% all grades) and anemia (20% all grades). Alectinib is approved by the FDA and the European Medicines Agency for first-line therapy of advanced/metastatic ALK+ NSCLC.

Several other ALK TKIs are being tested in the first-line setting. The ALTA-1L study (NCT02737501) comparing the efficacy of brigantinib versus crizotinib has completed accrual. Ensartinib (eXalt3; NCT02767804) and lorlatinib (NCT03052608) are also being tested against crizotinib in patients with treatment-naïve ALK+ lung cancer. The issue with many of these studies is that they began enrollment before the global ALEX trial was reported.

**Second-Line ALK Inhibitor Therapy and Beyond**

Since crizotinib was the first ALK TKI studied and approved, most of the available data to date focus on the efficacy of second- and third-generation ALK inhibitors (Table 1) in patients with acquired resistance to crizotinib. This topic has been reviewed extensively in the literature\(^{42,43}\) and for sake of space constraints and also relevance (with the emergence of first-line ceritinib and alectinib), will only be reviewed briefly here. In general, the factors that are important for selection of a second-line ALK TKI for a patient with acquired resistance to crizotinib are systemic activity, CNS activity, safety/adverse events profile, and resistance profiles. At present, ceritinib,\(^{44,45}\) alectinib,\(^{46}\) and brigantinib\(^{48,49}\) are all FDA approved for patients who are intolerant of or have experienced disease progression with crizotinib. Response rates range from approximately 40% to 60% across the studies, with mPFS of approximately 5 to 15 months depending on the study. Each of these inhibitors has documented CNS activity as well.

With the emergence of second-generation inhibitors, such as ceritinib and alectinib, in the first-line setting of metastatic ALK+ NSCLC, it is not precisely clear what standard of care will emerge for second-line treatment after acquired resistance to one of these more potent ALK TKIs. It is beneficial to understand acquired resistance to these inhibitors to develop rational therapeutic strategies at the time of disease progression. As seen with other TKIs in clinical use, resistance mechanisms encompass two broad categories—“on-target” mechanisms (such as kinase domain mutations and genomic amplification of the ALK fusion) and “off-target” mechanisms (predominantly “bypass” signaling pathways). Here, we will focus on overcoming “on-target” resistance mechanisms (“off-target” resistance mechanisms will be explored in greater detail below). Although current data sets are limited, at the time of acquired resistance to second-generation ALK TKIs, ALK kinase domain mutations will be detected in approximately 50% of drug-resistant tumors. In contrast to the experience with EGFR-mutant lung cancer, where T790M is the dominant (more than 60%) resistance mutation,\(^{7,8}\) many different ALK resistance mutations...
(such as C1156Y, I1171T/N/S, F1174L/C, V1180L, R1192P, L1196M, G1202R, D1203N, S1206Y/C, E1210K, A1280V, G1269A, and others) have been described.50,51 Of these mutations, the G1202R solvent front mutation is thought to be the most recalcitrant mutation, with increasing frequency of this mutation detected with increased “on-target” potency of the ALK inhibitor.

Lorlatinib is a third-generation ALK TKI, which was designed to be increasingly selective/potent against ALK and have increased brain penetration (lorlatinib is also an ROS1 inhibitor as described in below). Lorlatinib has activity against most known ALK kinase domain mutations, including G1202R.52 Initial reports from the ongoing international phase I trial of lorlatinib (NCT01970865) have recently been published.53 Forty-one patients with ALK+ NSCLC received at least one dose of lorlatinib, 52% of whom had received two or more prior TKIs and 72% had documented CNS metastases. The ORR was 46% (95% CI, 31%–63%) for all patients who were ALK+ and 42% for those patients who had received two or more prior ALK TKIs. Adverse effects of lorlatinib included hypercholesterolemia (72% across the entire study), hypertriglyceridemia (39%), peripheral edema (39%), and peripheral neuropathy (39%). Neurocognitive adverse events (slowed speech, slowed mentation, and word-finding difficulty) were also observed, although the precise frequency was not defined.

More recently, the results from the phase II lorlatinib study were presented.54 This trial included five cohorts of patients with ALK+ NSCLC (and a sixth cohort for ROS1). In cohort 1 (30 patients who were ALK+ treatment naive), the ORR was 90%, and the intracranial ORR was 75%. In cohorts 2 (27 patients) and 3A (32 patients; cohorts 2 and 3 included patients who were ALK+ and had previously received crizotinib only [cohort 2] or crizotinib with or without chemotherapy [cohort 3A]), the ORR was 69%, and the intracranial ORR was 68%. In cohort 3B (28 patients who were ALK+ and had previously received a noncrizotinib ALK inhibitor with or without chemotherapy), the ORR was 33%, and the intracranial ORR was 42%. In cohorts 4 (65 patients) and 5 (46 patients; cohorts 4 and 5 included patients who were ALK+ and had previously received two prior TKIs [cohort 4] or three prior TKIs [cohort 5] with/without chemotherapy), the ORR was 39%, and the intracranial ORR was 48%. These studies led the FDA to give lorlatinib breakthrough therapy designation for the treatment of patients with ALK+ metastatic NSCLC previously treated with one or more ALK inhibitors.

Rational Combination Strategies to Improve Outcomes for Patients With ALK-Rearranged Lung Cancers

Resistance to ALK TKI therapy also can be mediated by numerous ALK-independent mechanisms, most commonly thought to be activation of “bypass” signaling pathways that circumvent the inhibited ALK fusion protein. Bypass signaling pathways that have been shown to occur clinically include EGFR pathway activation,55 IGF-1R pathway activation,56 SRC signaling,57 cKIT amplification,55 and MAPK pathway activation (via KRAS copy number gain or loss of the phosphatase DUSP658). Histologic changes, such as epithelial to mesenchymal transition59 and transition to small cell lung cancer,59 have also been described. Several ongoing clinical trials hope to address the proper sequence of ALK TKIs and the role of rational combination therapies to maximize benefit and outcomes for patients with ALK+ NSCLC. For example, the combination of ceritinib and the allosteric MEK inhibitor, trametinib, is being tested in an ongoing phase I/II trial (NCT03087448). Ceritinib is also being evaluated in combination with the CDK4/6 inhibitor ribociclib/LEE011 (NCT02292550).60 Finally, ALK TKIs are being tested in combination with immune checkpoint inhibitors; however, retrospective data suggest that the magnitude of benefit seen in this cohort of patients with ALK+ NSCLC treated with checkpoint inhibitors is small.61 Additional rational study designs to forestall or overcome ALK TKI resistance are urgently needed.

OTHER TARGETABLE GENOMIC ALTERATIONS IN PATIENTS WITH LUNG CANCER

ROS1 Rearrangements

Approximately 1% of lung adenocarcinomas are driven by oncogenic ROS1 rearrangements.62 The ROS1 and ALK kinase domains show considerable homology, explaining crizotinib’s high affinity for both.63 In the phase I PROFILE 1001 study, among 50 patients with ROS1-rearranged NSCLC, the ORR was 72% with a disease control rate of 90%, and mPFS reached 19.2 months.63 In a prospective phase II study and a retrospective EURO51 study, mPFS times were 10 and 9.1 months respectively, with ORRs of 72% and 80%, respectively.64,65 In a larger Asian phase II study, mPFS in 127 patients was 13.4 months.66 These studies led to crizotinib approval by the FDA (March 2016) and the European Medicines Agency (August 2016) for treatment of advanced ROS1-rearranged NSCLC.

Ceritinib is a second-generation ALK TKI that also has efficacy against ROS1. In a Korean phase II study, among 32 patients with ROS1 rearrangement (all crizotinib naive except for two patients), the ORR was 67%, and mPFS reached 19.3 months; however, clinical response was not observed in the two patients who had received crizotinib.67 Other ALK TKIs—including brigatinib and lorlatinib—have shown potential anti-ROS1 activity in early development studies.68 Among three patients treated with brigatinib, the patient who was crizotinib naive had a partial response (ongoing at 21.6 months), and in 12 patients treated with lorlatinib (seven were crizotinib pretreated), the ORR was 50% with an mPFS of 7.0 months.69,70 Other potential ROS1 inhibitors include entrectinib (a potent inhibitor of ALK, ROS1 kinase, and TRK), which was evaluated in 14 patients who were crizotinib naive (13 with NSCLC and one with melanoma) in two phase I studies, giving an ORR of 86% (no responses in six patients who were pretreated with crizotinib) and an mPFS of 19 months.71 Preliminary results from a Japanese phase I study of DS-6051b
(a ROS1/TRK inhibitor) gave an ORR of 62.5% among 13 patients with NSCLC (no responses in three patients who were pretreated with crizotinib).70

The most common mechanism of resistance to crizotinib in ROS1+ NSCLC is mediated by the ROS1 Gly2032Arg mutation, analogous to ALK Gly1202Arg.50 Second-generation ALK TKIs with ROS1 activity (ceritinib, brigatinib, and entrectinib) are ineffective against ROS1 Gly2032Arg. Lorlatinib retains potent activity against ROS1 Gly2032Arg in vitro and in vivo.52 Research is needed to assess its efficacy in ROS1+ patients who have relapsed after treatment with available TKIs.

**BRAF Mutations**

The most common BRAF mutation, V600E (Val600Glu), is observed in 1% to 2% of lung adenocarcinomas.1,71 In the phase II VE-BASKET trial with vemurafenib including patients with various BRAFV600-mutant tumors, the ORR and the mPFS in an NSCLC cohort of 19 patients were 42% and 7.3 months, respectively.72 In a recent phase II study of dabrafenib as monotherapy or combined with trametinib in patients with BRAFV600-mutant metastatic NSCLC (BRF113928), dabrafenib monotherapy gave a 33% ORR in 78 pretreated patients with a median duration of response of 9.6 months and an mPFS of 5.5 months.73,74 The BRAF-MEK TKI inhibitor combination doubled the clinical benefit in 57 pretreated patients, with an ORR of 63% and an mPFS of 10.2 months.75 The combination showed similar benefits in 36 nonpretreated patients with BRAFV600E, with an ORR of 64% and an mPFS of 10.8 months. Median overall survival was prolonged in the two combination cohorts (18.2 and 24.6 months in pretreated and nonpretreated cohorts, respectively).76 The European Medicines Agency (April 2017) and the FDA (June 2017) have approved dabrafenib in combination with trametinib for treatment of BRAFV600E-mutant advanced NSCLC.

For non–BRAFV600-mutant NSCLC, six patients received BRAF inhibitors in the retrospective study.77 All tumors with non–BRAFV600E mutant located outside the activation segment of the BRAF kinase domain (codons 596–600) were refractory to BRAF inhibitors. However, one patient with a G596V mutation achieved a partial response to vemurafenib. Additional studies are needed to assess the benefit of immune checkpoint inhibitors in patients with BRAFV600E mutants and also assess if patients with non–BRAFV600E-mutant tumors can benefit from targeted therapies and/or immune checkpoint inhibitors. The current recommendation is to treat patients with BRAFV600E mutant with a BRAF-MEK inhibitor combination.

**RET Rearrangements**

RET fusions are found in 1% to 2% of NSCLCs and tend to be mutually exclusive with other oncogenic drivers.78 KIF5B-RET is the most common, with at least 10 fusion variants. Although RET-selective TKIs have not yet been developed, several multitarget agents with anti-RET activity have been evaluated that might be restricted in their ability to inhibit RET relative to their other kinase targets. The activity of multikinase inhibitors (cabozantinib, vandetanib, sunitinib, sorafenib, alectinib, lenvatinib, nintedanib, ponatinib, and regorafenib) in RET-rearranged NSCLC (ORR = 16%–47% and mPFS = 2.3–7.3 months) is clearly inferior to that seen with selective TKIs in other oncogene-addicted NSCLC models.79-81 The activity of cabozantinib in a phase II trial in RET-rearranged tumors was comparable with monotherapy BRAF TKIs in BRAFV600E mutant, with an ORR of 28% and an mPFS of 5.5 months, but clearly inferior to combination BRAF plus MEK TKIs.82 Other RET-specific TKIs are under development, and evaluation of alternative signaling pathways is needed for combination therapies to overcome RET resistance and determine the best strategies in this population.

**MET Alterations**

Dysregulation of the MET pathway occurs through protein overexpression, gene amplification, mutation, and rearrangement. Several agents (TKIs or monoclonal antibodies) have been developed to target MET or its ligand, hepatocyte growth factor. Early trials focused on targeting MET overexpression (15%–70% in unselected NSCLC) but without a consensus on the definition of MET positivity. MET overexpression has been particularly associated with blocking the EGFR pathway, leading to phase II/III combinations. Two randomized phase III trials failed to show any clinical benefit in OS of onartuzumab or tivantinib in association with erlotinib in unselected patients or MET protein–overexpressing NSCLC.83,84 Somatic MET mutations are diverse and include exon 14 skipping. The resulting mutant receptor shows increased MET signaling (truncated MET receptor leading to decreased ubiquitination and degradation of the MET protein). The diversity of MET exon 14 alterations presents challenges for diagnostic testing. MET exon 14 alterations are detected in 3% to 4% of NSCLCs, more frequently in adenocarcinoma and sarcomatoid histologic subtypes.84 Approximately 20% to 30% of sarcomatoid carcinomas harbor MET exon 14 alterations. Case reports and cohorts have shown dramatic and durable partial responses with MET-targeting TKIs including crizotinib, capmatinib, and caboazatinib in patients with MET exon 14. Preliminary data from the phase I trial of crizotinib (PROFILE 1001) evaluating patients with advanced lung cancer with MET exon 14 alterations showed an ORR of 44%, and global retrospective series showed an mPFS of 7 months.85 A small series has shown few responses to immunotherapy, even in patients with PD-L1 greater than or equal to 50%.86

MET amplification causes protein overexpression and constitutive kinase activation. MET copy number gains arise from two distinct processes: polysomy and amplification. They are identified by fluorescence in situ hybridization, showing an increase in the MET to CEP7 ratio, although no clear consensus on the definition of MET positivity based on gene copy number has been reached. MET amplification occurs via acquired EGFR TKI resistance, representing bypass track signaling (5%–20% of cases) or de novo (1%–5%).87 Crizotinib and capmatinib (INC280) have shown a potential
clinical benefit in small phase I/II trials on MET amplification (MET/CEP7 greater than or equal to 5), with ORRs of 67% and 47%, respectively, that must be confirmed.88,89 Clinical trials focusing on combined MET and EGFR TKIs for patients with acquired resistance to EGFR TKIs are ongoing. Encouraging antitumor activity has been seen with combined osimertinib and savolitinib (a selective MET TKI) in EGFR-mutated and MET-amplified patients (confirmed centrally by fluorescence in situ hybridization; MET gene copy greater than or equal to five or MET to CEP7 ratio greater than or equal to two; the TATTON trial).28 The ORR in patients who are T790M− was 53%, and duration of response was not reached.

**ERBB2/HER2 Alterations**

The ERBB2 gene encoding HER2 is a major proliferative driver activating downstream signaling via the PI3K-AKT and MEK-ERK pathways. Aberrations in HER2 have emerged as oncogenic drivers and therapeutic targets in lung cancers, with HER2 mutations (exon 20) in 1% to 5% and HER2 amplifications in 2% to 5% of lung adenocarcinomas. Kinase domain mutations, mainly exon 20 insertions and point mutations, lead to constitutive HER2 kinase activation.90 Although the clinical relevance in NSCLC is questionable given the lack of definition of HER2 positivity in this indication, several case reports have shown responses with HER2 TKIs in patients with an HER2 mutation, including afatinib, lapatinib, neratinib, and neratinib plus temsirolimus.91-93 Clinical benefit is generally low: for example, only three of 26 patients with HER2 mutant had a response (ORR of 12%) with dacomitinib and neratinib, and neratinib plus temsirolimus.91-93 Clinical benefit is also shown with larotrectinib, a selective pan-TRK inhibitor with an ORR of 76% (95% CI, 62%-87%) in 50 patients (7% lung cancer), regardless of type of tumor and NTRK rearrangement (NTRK1/2/3).101

**DISCUSSION**

The rapid development of genomic biomarkers that define various molecular subtypes of NSCLC (Fig. 1) and the spectrum of currently available targeted therapies against these targets (Table 1) have completely reshaped the treatment paradigm for oncogene-addicted cancers. Nonetheless, several major challenges still remain in this field.

A major challenge is making molecular testing available to the maximum number of patients. Successful implementation of personalized medicine requires widely accessible tumor molecular profiling in routine practice settings worldwide along with molecular centers for high-quality testing. Promising examples of large-scale routine molecular profiling on a national level have been reported as part of large cooperative networks in France and the United States, and they have included thousands of patients with NSCLC18 (Fig. 1B). It was encouraging to see that survival was improved for patients treated with biomarker-directed targeted therapies, showing the benefit of this treatment approach. Targeted gene sequencing or whole-exome sequencing by next-generation sequencing assays is gradually being integrated into clinical practice. Their success depends on them being made broadly available to practicing clinicians, applicable to small tumor biopsies, and affordable to patients and/or the health care system with a turnaround time to obtain results that is short. An emerging option is the use of plasma genotyping with sequencing circulating tumor DNA (including the detection of high tumor mutational burden as a potential biomarker for immunotherapy), which has the logistical advantage of being rapid, noninvasive, cheap, and nononeros for the patient.104,105 It is expected to become a new standard in daily clinical practice in the near future but still needs standardization, especially for the use of a large panel of genes. By carrying out increasingly extensive molecular analyses, many uncommon or rare alterations are detected for which clinical significance assessment constitutes a real challenge.
Nevertheless, the generation of massive volumes of data highlights that tools to support the medical interpretation and interaction between clinicians and scientists must be developed to ensure a thorough and rapid outcome. The implementation of molecular tumor boards both within hospitals and as national networks is increasingly widespread, offering an environment for discussion of all of these elements and dissemination of standardized practices and shared knowledge.

Another means of promoting wide access to genetic profiling is via innovative protocol designs, including molecular screening and both targeted therapy and immunotherapy arms for a single disease (umbrella trials) or a single targeted therapy for multiple diseases (basket trials). Examples of umbrella trials in advance NSCLC include the Lung-MAP (NCT02154490) for squamous cell carcinoma and the phase II trials Lung Matrix trial (NCT02664935), NCI-MATCH cooperative group trial (NCT01306045), and SAFIR02 lung trial (NCT02117167) for squamous and nonsquamous NSCLCs. In the SAFIR02 lung trial, high-throughput molecular analyses (comparative genomic hybridization array and next-generation sequencing) are used to evaluate whether treatment with guided targeted

![FIGURE 1. Molecular Cohorts of Lung Cancer](image)

(A) In a large academic center, these are the actionable mutations prospectively identified on a next-generation sequencing mutation platform (430 genes) over a set time period.103 (B) In a national molecular testing effort, these are the actionable mutations (six-gene panel) prospectively identified over a set time period.1

Abbreviation: WT, wild-type.
agents or immune checkpoint inhibitors improves clinical benefit compared with standard maintenance therapy in patients with metastatic NSCLC. For the basket trials, examples include the vemurafenib trial for BRAFV600-mutant patients, the French national AcSé trial (biomarker-driven access to crizotinib in ALK+, MET+, or ROS1+ malignancies in adults and children), the Larotrectinib (Loxo-101; a selective TRK inhibitor in patients with NTRK fusion cancer), and the recently published trial in HER2- and HER3-mutated patients.4,72,94,101

Another major challenge is that—despite the high response rates—all targeted therapies remain effective for a finite period of time. Improvements in outcomes for our patients will build on what we understand about how cancers escape targeted therapies (Fig. 2). One strategy is to improve on target inhibition. As has been seen in ALK+ lung cancers and EGFR-mutant lung cancers, better inhibitors can and have been developed. We have seen marked improvements in progression-free survival when we compared first-line treatment with newer agents, such as Alecensa and osimertinib compared with crizotinib and erlotinib/gefitinib.19,106

Alternative dosing schedules, such as pulse dosing of targeted therapy, can be explored, especially in the setting of trying to improve CNS penetration and efficacy.107 Dual target inhibition, such as the use of afatinib and cetuximab (an EGFR TKI and an EGFR antibody, respectively), can be used for maximum on target inhibition.9,10

Rational combination treatments that address known mechanisms of resistance should be assessed at the time of disease progression or at initial treatment to attempt to reverse or prevent acquired resistance. Many combinations are being studied in each of the molecular subsets of lung cancer. To truly personalize medical care, it is essential to sample the tumor at the time of acquired resistance by either tumor biopsy or analysis of plasma-derived sequencing circulating tumor DNA to identify the relevant resistance mechanisms for a particular patient. Finally, we must understand how alternative treatments, such as standard cytotoxic chemotherapy and immunotherapy, fit in when sequencing treatments for patients. There are some data to suggest that some of the oncogene-driven lung cancers are less responsive to immunotherapies,61 which makes it even more important to identify in whom and when to use immunotherapy. We also can use information regarding concurrent molecular alterations to provide both prognostic and predictive information. Although the majority of patients appropriately selected have excellent responses to targeted therapies, there are clearly outliers who have primary progression or shorter limited responses to targeted therapies. If certain concurrent alterations can identify these poor responders, we can focus efforts on developing new strategies to improve outcomes for these patients.

Overall, the prospective identification and rational therapeutic targeting of oncogenic “driver” mutations have paved the way for implementing precision treatment strategies in NSCLC and are now the standard of care worldwide. Despite much success in this area, a large amount of work is still needed to optimize the effectiveness of these therapies for patients with lung cancer and understand how to best sequence our available treatments. Collaborative efforts and integration of mutational data with multiomic, functional, and clinic-pathologic data are critical steps for the future to

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**FIGURE 2. Mechanisms of Acquired Resistance to Targeted Therapies**
advance our understanding of lung oncogenesis and hopefully, turn oncogene-driven lung cancer into a chronic manageable disease state.

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H. A. Yu, D. Planchard, and C. M. Lovly contributed equally to this article.

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MELANOMA/SKIN CANCERS
New Era in the Management of Melanoma Brain Metastases

Hussein A. Tawbi, MD, PhD, Celine Boutros, MD, David Kok, MBBS, Caroline Robert, MD, PhD, and Grant McArthur, MBBS, PhD

OVERVIEW

The remarkable advances in the systemic therapy of metastatic melanoma have now extended the 1-year overall survival rate from 25% to nearing 85%. Systemic treatment in the form of BRAF-targeted therapy and immunotherapy is slowly but surely proving its efficacy in the treatment of metastatic brain metastases (MBM). Single-agent BRAF inhibitors provide an intracranial response rate of 25% to 40%, whereas the combination of BRAFi/MEKi leads to responses in up to 58%. However, the durability of responses induced by BRAFi/MEKi seems to be even shorter than in extracranial disease. On the other hand, single-agent ipilimumab provides comparable clinical benefit in MBMs as it does in extracranial metastases. Single-agent PD-1 antibodies induce response rates of approximately 20%, and those responses appear durable. Similarly the combination of CTLA-4+ PD-1 antibodies induces durable responses at an impressive rate of 55% and is safe to administer. Although the local treatment approaches with radiation and surgery remain important and are critically needed in the management of MBM, systemic therapy offers a new dimension that can augment the impact of those therapies and come at a potentially lower cost of neurocognitive impairment. Considerations for combining those modalities are direly needed, in addition to considering novel systemic combinations that target mechanisms specific to MBM. In this report, we will discuss the underlying biology of melanoma brain metastases, the clinical outcomes from recent clinical trials of targeted and immunotherapy, and their impact on clinical practice in the context of existing local therapeutic modalities.

Cutaneous melanoma is an aggressive skin malignancy with an increasing incidence worldwide.1,2 In the United States alone, an estimated 1.1 million people were living with melanoma of the skin in 2014.3 Although melanoma brain metastases (MBM) are the third-most-common origin of metastases to the brain after lung and breast cancers, melanomas exhibit the highest level of cerebral tropism of all cancer types; 40% to 50% of patients with stage IV disease develop brain metastases.4,5 Historically, patients with MBM had uniformly dismal outcomes, especially fatal complications of a disease for which the median overall survival was 7 to 9 months. The remarkable advances in the systemic therapy of melanoma have extended the 1-year overall survival rate of metastatic melanoma from 25% historically to almost 85% now. Systemic treatment in the form of BRAF-targeted therapy and immunotherapy is slowly but surely proving its efficacy in the treatment of MBM and leading to median overall survival times of 14 to 23 months.6,7 Although the local treatment approaches with radiation and surgery remain important and are critically needed in the management of MBM, systemic therapy offers a new dimension that can augment the impact of those therapies and come at a potentially lower cost of neurocognitive impairment.

Here, we discuss the underlying biology of MBM, the clinical outcomes from recent clinical trials of targeted and immunotherapy, and the impact of trial outcomes on clinical practice in the context of existing local therapeutic modalities.

THE BIOLOGY OF BRAIN METASTASES

Melanoma shares with other cancers the fundamental steps in the metastatic cascade that lead to the establishment of distant metastases; namely, embolization of tumor cells through the systemic circulation, arrest in the cerebral microvasculature, extravasation, and colonization of the parenchyma. However, melanomas possess numerous intrinsic genomic mechanisms that specifically facilitate each of these steps in cerebral tissue and thus predispose to the establishment of brain metastases. In addition, the unique cerebral microenvironment presents both opportunities and challenges to the establishment and treatment of MBM.

Localization and Extravasation of Melanoma Cells Into the Brain

Formation of MBM begins with the arrival of melanoma cells in the brain vasculature. This can occur passively—through simple physical impaction at microvasculature
branch points—or actively, when melanoma cells preferentially adhere to the cerebral endothelium.9,10

The molecular mechanisms that promote this adherence are only just becoming understood, but the effector molecules are increasingly being identified. One such group is the chemokine proteins and their membrane-bound receptors. These normally play a key role in the regulation of physiologic cell migration and homing.11,12 In particular, chemokine receptor type 4 (CCR4) is a seven-transmembrane receptor that is overexpressed in melanoma cells that metastasize to the brain, and it is strongly predictive for MBM formation in mouse models.13,14 Activation of CCR4 phosphorylates the brain, and it is strongly predictive for MBM formation that is overexpressed in melanoma cells that metastasize to the brain parenchyma, and it is strongly predictive for MBM formation

After melanoma cells have arrested in the brain microvasculature, they are faced with the unique protective interface known as the blood-brain barrier (BBB). The BBB is composed of two functional layers: first, endothelial cells affixed together by tight junctions, and, second, an underlying basement membrane composed of extracellular matrix. This effectively restricts the passage of most compounds between the vasculature and the brain parenchyma.18

Melanomas have mechanisms to overcome both protective layers. The secretion of serine proteases breaks down endothelial tight junctions. These proteases disrupt the transmembrane proteins occludin and claudin-5 as well as the cytoplasmic plaque protein ZO-1.10 Melanoma cells then release the extracellular matrix degrading enzymes MMP-2 and heparanase to degrade the basement membrane.19 MMP-2 is seen in many cancer pathologies, but the neurotrophin-heparanase pathway is both brain and melanoma specific. Neurotrophin receptor p75NTR is highly expressed on the surface of melanoma cells.20,21 Activation of this receptor by neurotrophins present in the intracranial compartment, such as nerve growth factor and brain-derived neurotrophic growth factor, stimulates the release of heparanase.22

Melanotransferrin also plays an important role in melanoma cell extravasation. It is a glycoprotein highly expressed in melanoma cells and has both a secreted and a membrane-bound form.23 Mouse models have shown that the ability of melanoma cells to cross the BBB was directly correlated with cell-surface expression of melanotransferrin.24 The molecular mechanism for this is not known, but melanotransferrin also is found in high concentrations in brain capillary endothelium,25 which suggests a possible cross-signaling mechanism.

**Intraparenchymal Migration and Growth**

After the BBB has been successfully breached, melanoma cells transmigrate into the brain parenchyma in a paracellular manner.26 Initially, they continue to access the necessary nutrients for growth and survival from the pre-existing microvasculature. Hence, growth and proliferation occur alongside the inner surface of the cerebral vessels in a process known as vessel co-option.9,26

As metastases continue to grow in size, neoangiogenesis is required to sustain them. One of the mechanisms of MBM neoangiogenesis is via the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Activation of STAT3 is significantly increased in melanoma brain metastasis compared with primary tissues. It in turn upregulates interleukin (IL)-23, which stimulates melanoma cells to secrete MMP-2, VEGF, and basic fibroblast growth factor (bFGF)—all of which play a role in parenchymal invasion and neoangiogenesis.27 The S100A4 protein, (a member of the S100 protein family commonly used in immunohistochemical stains) also is a promoter of parenchymal invasion by melanoma cells28 and has been shown to synergistically stimulate neovascularization with VEGF.29 Numerous other angiogenic genes, including **CECAM1, PECAM1, HSPG2** and **CXCL10**, have been noted to be highly upregulated in non-melanoma brain metastases,30 although whether they are specifically involved in MBM is still undetermined.

**Role of the PI3K/AKT and Mitogen-Activated Protein Kinase Pathways in Brain Metastases**

The PI3K/AKT and mitogen-activated protein kinase (MAPK) pathways are two parallel pathways that regulate cell survival and proliferation. Activation of the PI3K/AKT pathway has been heavily implicated in the promotion of MBM: multiple studies reported significantly higher levels of phosphorylated AKT (pAKT) and lower levels of PTEN (an inhibitor of AKT) in MBM compared with extracranial metastases.31,32

The PI3K/AKT pathway facilitates multiple steps in the formation of MBM via cross-signaling and upregulation of the previously mentioned molecules CCR4, heparanase, VEGF, and STAT3.14,33,34 AKT also phosphorylates Cx43 that in turn promotes melanoma cell extravasation and co-option of blood vessels.35

The MAPK pathway also may be associated with brain metastases. In a study that prospectively observed patients with primary melanoma, there appeared to be some association of **BRAF** mutations with the development of brain

<table>
<thead>
<tr>
<th>PRACTICAL APPLICATIONS</th>
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<tr>
<td>• Brain metastases are a common clinical problem in patients with melanoma.</td>
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<td>• Local therapeutic modalities offer control of oligometastatic disease but have no impact on brain metastases—free survival or extracranial disease.</td>
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<tr>
<td>• Systemic therapy with <strong>BRAFi</strong> and <strong>BRAFi</strong>/<strong>MEKi</strong> offers high response rates but with curtailed durability compared to extracranial disease</td>
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<tr>
<td>• Immunotherapy is safe and offers durable responses in MBM; response rates are higher with combination therapy (anti-CTLA-4+, anti-PD-1) than either agent alone.</td>
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<tr>
<td>• Combination approaches of immunotherapy with radiation therapy have the potential for synergy but will need to be studied further to characterize the optimal sequence and timing.</td>
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metastases. There are no known molecular mechanisms that biologically link BRAF/MAPK pathway upregulation to specifically increase MBM formation although crosstalk to the PI3K pathway is possible.\textsuperscript{37} Interestingly, downregulation of the MAPK pathway by BRAF and MEK inhibition may lead to resistance by upregulation of the parallel PI3K/akt pathway.\textsuperscript{38,40} Hence, melanomas that acquire resistance may be particularly selected for intracranial progression, which may explain in a recent clinical study why the duration of clinical response to BRAF and MEK inhibition was half that of extracranial sites\textsuperscript{41} and why the brain is a dominant site of treatment failure after BRAF inhibition.\textsuperscript{41,42}

Role of the Brain Microenvironment

The brain microenvironment affects the formation and growth of MBM through multiple bidirectional mechanisms. These tumor-microenvironment interactions mean that both partners are to some extent responsible for regulating and shaping the phenotype of the other.

Astrocytes in cerebral tissue produce numerous regulatory signaling molecules as part of their normal homeostatic regulation of the intracranial environment. When these come into contact with MBM cells, they can have prometastatic effects. For example, astrocytes secrete a base level of neurotrophins that can bind to and activate neurotrophin receptors on MBM (as previously discussed).\textsuperscript{20} In addition, astrocytes secrete microRNAs that epigenetically downregulate PTEN and so upregulate the PI3K/akt pathway.\textsuperscript{43}

Upon invasion of the brain parenchyma by malignant cells, there is an active release of prometastatic molecules into the brain microenvironment. This is because invading MBM are seen as a traumatic brain insult by astrocytes, which then coordinate a neural regeneration response\textsuperscript{44} that releases heparanase, chemokines, and IL-23\textsuperscript{45} and increases concentrations of neurotrophins.\textsuperscript{45} Conversely, activated astrocytes release antineoplastic agents, including plasmin, that ultimately trigger apoptosis in the invading metastatic cells via the release of Fas ligand.\textsuperscript{46} Thus, there is a delicate push-and-pull balance of astrocyte-mediated factors that ultimately determines the success of MBM colonization.

Adding to this complexity are the immunoregulatory systems at play in the brain. In most healthy adults, an intact BBB restricts the entry of T cells into the brain parenchyma. However, T cells enter the brain when there is pathologic breakdown of the BBB by MBM. In fact, in one study, MBM were correlated with the highest concentration of tumor CD3\textsuperscript{\textsuperscript{\textsuperscript{47}}}, CD8\textsuperscript{\textsuperscript{47}}, and PD-1-positive T cells compared with all other brain metastasis pathologies.\textsuperscript{37} These effects likely are counterbalanced by immunosuppressive molecules, such as indoleamine-pyrole, 2,3-dioxygenase (IDO), PD-L1, and tumor growth factor beta, present in primary and/or metastatic brain tumors.\textsuperscript{48,49} The only one of these that has been explored in detail in MBM is PD-L1 expression, which was present in approximately 50% of MBM but, interestingly, was not correlated with CD3 or CD8 infiltration.\textsuperscript{47,50}

Biologic Implications on Current and Future Treatment Strategies

The unique biology of MBM necessitates an organ-specific approach when thinking of current and future treatment strategies. In the first instance, the potential for the physical restriction of the BBB to prevent drug and T-cell access to intraparenchymal lesions must be addressed, because this in theory could limit the effectiveness of both targeted agents and checkpoint inhibitors. Although pathologic breakdown of the BBB undoubtedly occurs with brain macrometastases, studies have demonstrated there is still intrasional and interlesional variation in drug concentrations after systemic administration.\textsuperscript{51,52} In addition, it is unclear if currently available therapies influence clinically undetectable micrometastases that may not be associated with BBB breakdown.\textsuperscript{53} Thus, development of specific BBB-permeable agents, or the addition of local therapies that compromise the BBB, are potential treatment strategies worthy of more research to potentially improve response rates.

Our ever-improving understanding of the molecular biology of MBM brings with it an increasing array of potential treatment targets. As a result of the vital role of STAT3 and s100A4 in MBM formation, inhibitors of STAT3 and s100A4 have promising early preclinical results.\textsuperscript{29,54} The neurotrophin-heparanase pathway also may present a worthwhile novel inhibitory target to reduce MBM. In vitro tests have demonstrated that introduction of microRNAs that target heparanase has reduced the adhesion, migration, and invasion of melanoma cells.\textsuperscript{55}

Finally, although we are only just starting to understand the immunoregulatory systems in the brain microenvironment, it is clear that immunomodulation has a key role to play in the management of MBM. Checkpoint inhibitors, including various combinations of anti–PD-1, anti–CTLA-4, and IDO inhibitors, present promising therapeutic opportunities for patients with MBM.

SYSTEMIC THERAPY OF MELANOMA BRAIN METASTASES

In the past decades, local therapies such as surgery, whole-brain radiation therapy, and stereotactic radiosurgery were considered the pillars of MBM management. Advances in understanding the biology and molecular pathways implicated in melanoma followed by the arrival of effective systemic therapies in extracerebral metastatic melanoma have generated considerable interest in evaluations of these novel systemic strategies, including targeted therapies and immunotherapy, in patients with brain involvement (Table 1).\textsuperscript{13}

Targeted Therapies

In the phase II BREAK-MB study, the BRAF inhibitor dabrafenib showed clinical activity and an acceptable safety profile in patients with BRAF V600E–mutant MBM.\textsuperscript{56} Among the 172 patients enrolled in the study, 74 patients had not received previous local treatment (cohort A) whereas 65 patients had (cohort B). The overall intracranial response was lower than that observed in extracranial disease but was...
independent of previous local treatment of brain metastases (in 39% and 31% of patients, respectively). In both cohorts, the median progression-free survival (PFS) was approximately 16 weeks, and the overall survival (OS) was approximately 31 weeks. Response rates seemed lower in the presence of \(\textit{BRAF} \text{V600K}\) mutation compared with \(\textit{BRAF} \text{V600E}\) (7% and 22% in cohorts A and B, respectively). Adverse events (AEs) were not different from those reported for extracranial disease; notably, intracranial AEs were very uncommon. Overall, 26% of patients had pyrexia of any grade and 6% had cutaneous squamous cell carcinoma. A phase II study of the BRAF inhibitor vemurafenib reported lower response rates, but similar PFS, in similarly defined patient cohorts.62

The combination of dabrafenib and the MEK inhibitor trametinib improved OS when compared with dabrafenib monotherapy in advanced melanoma without brain metastases.63,64 Similarly, this combination was evaluated in patients with \(\textit{BRAF} \text{V600}–\text{mutant MBM}\) in the phase II COMBI-MB study.41 Among the 125 patients enrolled, 76 patients had \(\textit{BRAF} \text{V600E}–\text{positive asymptomatic MBM, no previous local brain therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (cohort A); 16 patients had }\textit{BRAF} \text{V600E}–\text{positive asymptomatic MBM, previous local brain therapy, and an ECOG of 0 or 1 (cohort B); 16 patients had }\textit{BRAF} \text{V600D/K/R}–\text{positive asymptomatic MBM with or without previous local brain

### TABLE 1. Review of Clinical Studies That Evaluate Systemic Therapies for Melanoma Brain Metastases

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<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Study Population</th>
<th>Treatment</th>
<th>Intracranial Response (%)</th>
<th>Median OS (Months)</th>
<th>Median PFS (Months)</th>
<th>Median Follow-Up (Months)</th>
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<tr>
<td>Long et al60</td>
<td>BREAK-MB (phase II)</td>
<td>Cohort A: no previous local treatment</td>
<td>Dabrafenib</td>
<td>Cohort A: 39</td>
<td>Longer than 31 weeks</td>
<td>Longer than 16 weeks</td>
<td>Not available</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cohort B: previous local treatment</td>
<td></td>
<td>Cohort B: 31</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Cohort A: (\textit{BRAF} \text{V600-E}, asymptomatic, no previous local treatment.)</td>
<td></td>
<td>Cohort A: 58</td>
<td>Cohort A: 10.8.</td>
<td>Cohort A: 5.6</td>
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<tr>
<td></td>
<td></td>
<td>Cohort B: (\textit{BRAF} \text{V600-E}, asymptomatic, with previous local treatment)</td>
<td></td>
<td>Cohort B: 56</td>
<td>Cohort B: 24.3</td>
<td>Cohort B: 7.2</td>
<td></td>
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<tr>
<td>Davies et al41</td>
<td>COMBI-MB (phase III)</td>
<td>Cohort C: (\textit{BRAF V600D/K/R, asymptomatic, with or without previous local brain therapy.})</td>
<td>Dabrafenib + trametinib</td>
<td>Cohort C: 44</td>
<td>Cohort C: 10.1</td>
<td>Cohort C: 4.2</td>
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<tr>
<td></td>
<td></td>
<td>Cohort D: (\textit{BRAF V600D/E/K/R, symptomatic, with or without previous local brain therapy.})</td>
<td></td>
<td>Cohort D: 59</td>
<td>Cohort D: 11.5</td>
<td>Cohort D: 5.5</td>
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<tr>
<td>Margolin et al57</td>
<td>BMS-734016 (phase II)</td>
<td>Cohort A: asymptomatic, without corticosteroids</td>
<td>Ipilimumab</td>
<td>Cohort A: 16</td>
<td>Cohort A: 7.0</td>
<td>Cohort A: 2.7</td>
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<td></td>
<td>Cohort B: symptomatic, with stable doses of corticosteroids</td>
<td></td>
<td>Cohort B: 5</td>
<td>Cohort B: 3.7.</td>
<td>Cohort B: 1.3</td>
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<tr>
<td>Di Giacomo et al58</td>
<td>NIBIT-M1 (phase II)</td>
<td>Asymptomatic</td>
<td>Ipilimumab + fotemustine</td>
<td>40</td>
<td>12.7</td>
<td>3.0</td>
<td>39.9</td>
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<tr>
<td>Goldberg et al59</td>
<td>Small phase II</td>
<td>Asymptomatic, untreated</td>
<td>Pembrolizumab</td>
<td>22</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Long et al61</td>
<td>ABC (phase II)</td>
<td>Cohort A: (\textit{BRAF} \text{V600E}, asymptomatic, no previous local treatment.)</td>
<td>Ipilimumab + nivolumab</td>
<td>Cohort A: 44</td>
<td>6-month data</td>
<td>6-month data</td>
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<td></td>
<td>Cohort B: disease failure after local therapy, or symptomatic</td>
<td></td>
<td>Cohort B: 20</td>
<td>Cohort A: 76%</td>
<td>Cohort A: 50%</td>
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<tr>
<td></td>
<td></td>
<td>Cohort C: (\textit{BRAF} \text{V600D/K/R, symptomatic, with or without previous local brain therapy.})</td>
<td>nivolumab</td>
<td>Cohort C: 6</td>
<td>Cohort B: 59%</td>
<td>Cohort B: 29%</td>
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<td></td>
<td>Cohort C: nivolumab</td>
<td></td>
<td></td>
<td>Cohort C: 44%</td>
<td>Cohort C: 0</td>
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<tr>
<td>Tawbi et al62</td>
<td>CheckMate 204 phase II</td>
<td>Asymptomatic</td>
<td>Ipilimumab and nivolumab</td>
<td>55</td>
<td>Not available</td>
<td>Not reached</td>
<td>6.3</td>
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</table>

Abbreviations: OS, overall survival; PFS, progression-free survival.
therapy and had an ECOG of 0 or 1 (cohort C); and 17 patients had BRAF V600D/E/K/R–positive symptomatic MBM with or without previous local brain therapy and had an ECOG of 0, 1, or 2 (cohort D). The primary endpoint was intracranial response in cohort A. An intracranial response was achieved in 58%, 56%, 44%, and 59% of patients in cohort A, B, C, and D respectively. In cohort A, the median PFS was 5.6 months, and the median OS was 10.8 months. AEs of any grade were observed in 98% of patients, and 48% reported one or more grade 3 or 4 AE. Altogether, the response rates were lower than those observed with the same treatment regimen in patients with extracranial disease (58% vs. 67%); remarkably, the median PFS was almost half (5.6 months vs. 10.1 months), which suggests an earlier treatment failure in the brain, as confirmed by a high rate of intracranial progression in more than two-thirds of patients who experienced disease progression.

**Immunotherapy**

Phase II and III studies have shown that ipilimumab is active in advanced melanoma and improves OS. A phase II study was conducted to evaluate ipilimumab in patients with MBM. Among the 72 patients enrolled in this study, 51 patients were neurologically asymptomatic and were not receiving corticosteroid treatment at enrollment (cohort A), whereas 21 were symptomatic and on a stable dose of corticosteroids (cohort B). The intracranial response was achieved in 16% and 5% of patients in cohort A and B, respectively. The median OS was 7.0 months in cohort A and was 3.7 months in cohort B. The most frequent grade 3 AEs were diarrhea, fatigue, dehydration, hyperglycemia, and increased concentrations of serum aspartate aminotransferase. This study confirmed the safety and intracranial efficacy of ipilimumab and highlighted the need for patients to be off of corticosteroids at the time of initiation of ipilimumab.

The combination of ipilimumab and fotemustine was evaluated in the phase II NIBIT-M1 study. Fotemustine, a chemotherapy historically used in Europe, where it is registered to treat patients with metastatic melanoma, is known to cross the BBB. Although fotemustine monotherapy is only poorly effective in metastatic melanoma (like other cytotoxic chemotherapies), a potential synergy with ipilimumab was hypothesized and evaluated in this clinical trial. Among the 86 patients included in the study, 20 patients had MBM; 40% of patients with asymptomatic brain metastases at baseline achieved an immune-related objective response. With a median follow-up time of 39.9 months, the median OS and the 3-year survival rates were 12.9 months and 28.5%, respectively, for the whole study population and were 12.7 months and 27.8%, respectively, for patients with brain metastases. Overall, 87% of the whole study population had all-grade AEs, whereas 55% had grade 3 or 4 AEs, and the most frequent was myelosuppression. Grade 3 or 4 elevation of alanine aminotransferase or aspartate aminotransferase was observed in 24% patients.

The follow-up phase III NIBIT-M2 study was initiated to evaluate fotemustine versus the combination of ipilimumab and nivolumab in patients with untreated, asymptomatic MBM (NCT02460068). Results of this study are pending.

The activity of pembrolizumab was evaluated in a small, phase II study, in which patients with melanoma or non–small cell lung cancer and untreated brain metastases were included. Among the 18 patients with melanoma who were treated with pembrolizumab, 22% achieved durable intracranial responses. The safety profile of pembrolizumab was acceptable, and AEs were primarily grade 1 or 2. Six percent of patients in the melanoma cohort had a grade 3 elevation of aminotransferases; 17% had clinically relevant neurologic AEs, which included transient grade 3 cognitive dysfunction and grade 1 or 2 seizures.

The activity of ipilimumab in combination with nivolumab versus nivolumab monotherapy in MBM was evaluated in the randomized phase II ABC study, which was based on the improved response rates and PFS rates associated with these drugs in clinical studies. Among the 76 patients enrolled in the study, 60 patients were asymptomatic and had not received previous local treatment of brain metastases, 35 received the combination of nivolumab and ipilimumab (cohort A), and 25 received nivolumab monotherapy (cohort B). Sixteen patients whose disease had failed to respond to local therapy or who were neurologically symptomatic and/or who had leptomeningeal disease received nivolumab monotherapy (cohort C). Intracranial responses were achieved in 44%, 20%, and 6% of patients in cohorts A, B, and C respectively. The 6-month OS rates were 76%, 59%, and 44% in cohorts A, B, and C respectively. The intracranial response rate in cohort A was 53% for treatment-naïve patients, but it was 16% in patients previously treated with BRAF inhibitors. Rates of grade 3 or 4 AEs in cohorts A, B, and C were 68%, 40%, and 56%, respectively.

The safety and efficacy of the combination of nivolumab and ipilimumab were evaluated in a larger population of patients in the phase II CheckMate 204 study. Here, 75 patients with asymptomatic MBM received the combination. With a median follow-up time of 6.3 months, the intracranial objective response rate was 56%. Overall, 19% of patients had a complete response, 37% had a partial response, and 8% had a stable disease for more than 6 months. Intracranial and extracranial responses were largely concordant. The median time to intracranial response was 2.8 months. With a median follow-up time of 9.2 months, the intracranial response rate was 55%, and this included a 21% complete response rate. The median PFS was not reached. The 6-month PFS was greater than 60%. AEs of any grade occurred in 96% of patients, and grade 3 or 4 AEs occurred in 52% of patients. No new or unusual central nervous system AEs were observed. Headache was the most frequent AE (in 25%), and it reached grade 3 or 4 in only 4% of patients. Results are pending after the enrollment of 119 patients, which included a small cohort (20 patients in cohort B) of patients who required corticosteroids at the time of initiation of therapy. CheckMate-204 and ABC independently confirmed that the combination of ipilimumab with nivolumab is safe and has a
high rate of durable intracranial responses in patients with asymptomatic MBM.

**Novel Combinations**

Novel combinations are being explored to increase the intracranial efficacy of systemic treatments with fewer AEs. The activity and safety of pembrolizumab combined with bevacizumab is being evaluated in a phase II study in patients with untreated brain metastases from melanoma or non–small cell lung cancer (NCT02681549). Similarly, the activity of atezolizumab combined with bevacizumab is being evaluated in patients with untreated MBM (BEAT-MBM study; NCT03175432); this study includes a cohort of patients who are asymptomatic or who require corticosteroids. Moreover, the intracranial efficacy of BMS-986205, an IDO inhibitor, combined with nivolumab in brain metastases (NCT02910700) and may be a potential therapeutic approach when combined with nivolumab in brain metastases to facilitate study designs as well as data analysis of objective response rates and PFS.

**Endpoints in Melanoma Brain Metastases Clinical Trials**

Immunotherapy may result in unusual responses manifested by an initial transient increase in tumor burden before response or by the appearance of new lesions in patients with responding baseline lesions. RECIST version 1.1, primarily developed to evaluate the responses to chemotherapies and targeted therapies, may not fully estimate the benefit of immunotherapy. Therefore, the immune-related response criteria were developed and include the bidimensional tumor measurement and the measurements of new target lesions into evaluation. Recently, immune-based therapeutics criteria (i.e., iRECIST) have been developed to provide consistency in design and data collection in immunotherapy studies and, ultimately, to validate guidelines. Unconfirmed progression requires confirmation, which includes an increase in the size or number of new lesions. This approach allows delayed responses that occur after pseudoprogression to be identified. Additional efforts have been made with the development of the immune-modified RECIST (i.e., imRECIST) that are based on data from atezolizumab studies. The imRECIST included unidimensional tumor measurement with up to five target lesions (two per organ, as per RECIST version 1.1). New lesions are added to the total tumor burden when measurable. Moreover, progression in nontarget lesions does not define progressive disease.

The measurement of intracranial responses adds another layer of complexity and requires special attention. A practical method that was used initially in BREAK-MB and subsequently used in COMBI-MB, CheckMate-204, and ABC, is to use a modified version of RECIST version 1.1 in which the brain is treated as a separate compartment; up to five lesions are measured (smallest > 5 mm on MRI) in addition to five extracranial lesions. In addition, recommendations for the evaluation of response and progression criteria of brain metastases in clinical trials have been developed by the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group. Two to five target lesions were allowed, provided that they had two perpendicular diameters greater than 10 mm. Complete response required the disappearance of all lesions for at least 4 weeks without corticosteroids. Partial response required a 30% or more decrease in the sum of the longest diameter of target lesions defined at baseline, sustained for at least 4 weeks, with stable or decreased doses of corticosteroids. Progressive disease was defined as 20% or more increase in the sum of the longest diameter of target lesions and at least one lesion that increased in size by 5 mm or more. An increase in corticosteroid doses without clinical deterioration did not indicate progression. These new radiologic criteria allow a uniform evaluation of immunotherapy responses and may facilitate study designs as well as data analysis of objective response rates and PFS.

**RADIATION THERAPY MODALITIES AND MELANOMA BRAIN METASTASES**

**Whole-Brain Radiation Therapy Versus Stereotactic Radiosurgery**

Radiation therapy with or without surgery has been the mainstay of treatment of patients with brain metastases of solid tumors. Whole-brain radiation therapy (WBRT) continues to be an important modality, but no randomized controlled trials have examined WBRT compared with best supportive care in melanoma. However, the QUARTZ study in non–small cell lung cancer did not show any benefit from WBRT, so the true impact of WBRT on brain metastases from melanoma is likely to be limited, which is not surprisingly given the DNA repair capacity of melanoma cells and the relative resistance to radiation. Although the efficacy of WBRT remains in question, its toxicity is well documented in the form of neurocognitive decline manifested by memory loss and impaired executive function. WBRT has been shown to impair cognition and induce an irreversible dementia-like state in some patients. This effect is becoming increasingly ominous as survival increases from central nervous system cancers in general and MBM in particular. Multiple interventions to mitigate the risk of WBRT-induced cognitive decline have been evaluated. The delivery of WBRT with conformal avoidance of the hippocampus was evaluated in a multi-institutional phase II study (RT0G 0933) and was indeed associated with preservation of memory and quality of life compared with historical controls (p < .001). Similarly, the addition of the N-methyl-d-aspartate receptor antagonist memantine to WBRT resulted in better cognitive function and a significantly longer time to cognitive decline.

The rapid uptake of stereotactic radiosurgery (SRS) in the 1990s revolutionized the care of patients with brain metastases and largely supplanted surgery for smaller asymptomatic lesions. In the case of melanoma, the lethal dose of radiation delivered with SRS appears sufficient to kill melanoma cells. In addition, SRS can spare specific regions, such as the hippocampus, thalamus, and brainstem, which may be important to preserve memory and quality of life.
as the optic nerves and hippocampus, and potentially mitigate negative cognitive effects of WBRT and/or conformal-field WBRT while producing 12-month local control rates of up to 75%.80-82 SRS can effectively lead to local control of established brain metastases, but its use is limited by the number of metastases present.83 Although many centers are treating multiple lesions now, the accepted standard and published literature supports the use of SRS for up to only three lesions. Therefore, SRS is preferred instead of WBRT as initial therapy for patients with MBM and oligometastatic disease; WBRT is reserved for recurrence after SRS, a large number of metastases, or leptomeningeal disease.

**Immunotherapy Combined With Radiation**

The potential synergy of radiation therapy with immunotherapy has been suspected for decades but has become an exciting arena for investigation after reports of the so-called abscopal effect and the advent of checkpoint inhibitors.84 This is even more likely to be relevant in the brain, when radiation is clinically indicated, and could improve the permeability of the BBB, increase antigen release and presentation, and increase the expression of inflammatory cytokines such as IL-1α, IL-6, and tumor necrosis factor alpha or VEGF.85 Knisely et al86 reported a retrospective MBM series in which patients treated with ipilimumab plus WBRT, compared with those treated with radiotherapy alone, achieved a longer median survival (21.3 vs. 4.9 months, respectively) and a greater 2-year survival rate (47.2% vs. 19.7%, respectively). Similarly, ipilimumab plus SRS increased the median OS from 5.3 to 18.3 months (p = .002), but not in patients who received ipilimumab plus WBRT (HR 0.56; p = .15) in a series of 70 patients with MBM treated at the University of Michigan. However, the addition of ipilimumab to SRS improved survival compared with SRS alone (median, 19.9 vs. 4.0 months; p = .009) and had no increase in central nervous system toxicity.87 Ahmed et al88 reported data from 26 patients who received nivolumab with SRS for MBM, which demonstrated safety and high rates of local (91%) and distant (53%) brain control at a median follow-up of 15 months. Although prospective studies to evaluate combinations of SRS and immunotherapy are ongoing, the optimal timing for the introduction of systemic therapy (before or after SRS) remains unclear, given the current established practice patterns in which SRS is pursued early in the management of MBM. Also, measures of changes of neurocognitive function with such combinations are imperative to clearly delineate the potential delayed additive toxicity as well as the potential increase in the rate of radiation necrosis.

**Targeted Therapy Combined With Stereotactic Radiosurgery**

Targeted therapy can decrease the size and number of MBM and therefore could render SRS more feasible and effective. However, there is no strong biologic rationale for potential synergy like there is with immunotherapy, beyond the immunologic impact of BRAF-directed therapy. Nonetheless, modern series indicate that the combination of targeted therapy with SRS, like the combination with immunotherapy, appears to improve overall outcome.89 An ongoing, phase II, open-label, prospective study (NCT01721603) is evaluating the effect of dabrafenib in combination with SRS on the 6-month distant brain metastasis–free survival rate compared with historical control (SRS alone).

**Radiation Necrosis**

Radiation necrosis (RN) is a potential delayed complication of radiation therapy that occurs in 11% to 19% of patients with brain metastases, and it appears more likely with SRS.90,91 RN typically develops 7 to 12 months after therapy and can be associated with great morbidity, including seizures, language impairment, psychomotor slowing, and sensorimotor deficits.92 With the increasing use of immunotherapy to treat cancers other than melanoma, there is a large need to better define RN, its true incidence, and its potential exacerbation, because its etiology appears highly rooted in the modulation of the immune response.

All currently available data to describe RN are retrospective case series that provide conflicting information. A retrospective review of 54 patients who received SRS showed no difference in the incidence of RN between patients who received or did not receive ipilimumab within 4 months of SRS.93 Conversely, among 180 consecutively treated patients who received SRS plus systemic therapy, with a median follow-up time of 11.7 months, RN incidence was significantly greater in patients who received immunotherapy compared with chemotherapy or targeted therapy (odds ratio, 2.40; 95% CI, 1.06 to 5.44; p = .03). Conversely, chemotherapy was associated with a lower risk of RN relative to other treatments (odds ratio, 0.38; 95% CI, 0.18 to 0.78; p = .01).94 Conflicting results were reported in 137 patients with MBM who were treated with SRS and systemic therapy at the MD Anderson Cancer Center. This study found that concurrent treatment with chemotherapy, larger size of lesions, and greater number of lesions treated were predictive of RN; however, immunotherapy and timing proximity to SRS were not associated with increased RN risk.95 Increased RN incidence also may be associated with the combination of BRAF inhibitors and SRS.96 Among 15 patients treated with targeted therapy before, after, or concurrent with SRS, efficacy endpoints were similar, but there was an increased incidence with BRAF inhibitors and SRS versus SRS alone of RN (22.2% vs. 11.0% at 1 year; p < .001) and of symptomatic RN (28.2% vs. 11.1% at 1 year; p < .001). These results highlight the need for a prospective evaluation of this morbid condition associated with SRS in the context of ongoing clinical trials of systemic agents in MBM.

**CONCLUSION**

Brain metastases are a common clinical occurrence in patients with metastatic melanoma and pose a unique set of challenges that range from a higher rate of mortality to devastating neurologic sequelae of the disease itself or the AEs of available therapies. Surgery and radiation therapy continue to be needed to treat large or symptomatic lesions, and
systemic targeted and immunotherapy agents are offering renewed hope for prolonged intracranial disease control that could decrease or delay the onset of neurocognitive decline and/or death.

Although BRAF-targeted therapy and combination immunotherapy with nivolumab and ipilimumab appear to have similar response rates, the higher rate of durable intracranial responses to combination immunotherapy suggests that this modality should be considered for first-line therapy, potentially along with radiation. BRAF-targeted therapy can be reserved for treatment failure or for patients who are either dependent on corticosteroids or unlikely to tolerate combination immunotherapy.

Prospective randomized clinical trials are needed to better delineate the optimal combinations of systemic agents with SRS. Those studies should include the meticulous collection of imaging data and neurocognitive assessments to fully characterize the impact of novel therapies.

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Emerging Strategies in Systemic Therapy for the Treatment of Melanoma

Paolo A. Ascierto, MD, Keith Flaherty, MD, and Stephanie Goff, MD

OVERVIEW

Recent years have seen major improvements in survival of patients with advanced melanoma with the advent of various novel systemic immunotherapies and targeted therapies. As our understanding of these agents and their various mechanisms of action improves, even more impressive outcomes are being achieved through use of various combination strategies, including the combining of different immunotherapies with one another as well as with other modalities. However, despite the improved outcomes that have been achieved in advanced melanoma, responses to treatment are heterogeneous and may not always be durable. Additional advances in therapy are required, and several emerging strategies are a focus of interest. These include the investigation of several new immunotherapy and/or targeted therapy combinations, such as checkpoint inhibitors (anti–PD-1/anti–CTLA-4) with other immunotherapies (e.g., indoleamine 2,3 dioxygenase [IDO] inhibitors, antilymphocyte activation 3 [anti–LAG-3], histone deacetylase [HDAC] inhibitors, Toll-like receptor 9 [TLR-9] agonists, antiglucocorticoid-induced tumor necrosis factor receptor [anti–GITR], pegylated interleukin-2 [IL-2]), combined targeted therapies (e.g., MEK and CDK4/6 coinhibition), and combined immunotherapy and targeted therapy (e.g., the triplet combination of BRAF/MEK inhibition with anti–PD-1s). The identification of novel therapeutic targets in the MAP kinase pathway also offers opportunities to improve outcomes by overcoming de novo and acquired resistance to BRAF/MEK inhibition (e.g., the development of ERK inhibitors). In addition, adoptive cell transfer, the infusion of large numbers of activated autologous lymphocytes, may have a potential role in patients whose disease has progressed after immunotherapy. Taken together, these new approaches offer further potential to increase systemic treatment options and improve long-term outcomes for patients with advanced melanoma.

Recent years have seen clinically important advances in the treatment of melanoma with the advent of various systemic immunotherapies and targeted therapies. Since 2011, several of these new agents have been approved and have resulted in improvements in the survival of patients with advanced melanoma. Even more impressive, outcomes are now being observed through the use of various combination strategies, including different immunotherapies being combined with one another as well as with other modalities. However, despite the major advances that have clearly been achieved in improving outcomes for patients with melanoma, responses to treatment are heterogeneous and may not always be durable.

As our understanding of these novel treatment approaches evolves, attempts to further improve outcomes for more patients are ongoing. This includes investigation of a wide range of novel treatment combinations together with the identification of new targets for therapy. Another approach, adoptive cell transfer (the infusion of large numbers of activated autologous lymphocytes), also offers potential, primarily as a treatment option for patients with disease progression after immunotherapy. Recent advances in these fields are reviewed and discussed here.

NOVEL COMBINATION THERAPIES

The development of novel treatments, in particular the immunomodulating monoclonal antibodies (anti–CTLA-4, anti–PD-1/PD-L1) and small molecule–targeted therapies (BRAF and MEK inhibitors), has revolutionized the prognosis for patients with advanced melanoma. However, although monotherapy with many of these agents has been shown to improve survival compared with previously available treatment options, even greater improvements are being seen with the use of various combination approaches. Improved outcomes have been observed with combined CTLA-4 and PD-1 versus monotherapy,1,2 with an overall 3-year survival rate of 58% with ipilimumab plus nivolumab,3 as well as with combined BRAF and MEK inhibitors.4,5 Now, several new doublet as well as triplet combinations are being investigated.
Immunotherapies

**Anti–PD-1 plus IDO inhibitor.** IDO1 is an interferon-gamma (IFN-γ)–induced intracellular enzyme that catalyzes the first and rate-limiting step of tryptophan degradation in the kynurenine pathway. In tumors, depletion of tryptophan and production of kynurenine and other metabolites shift the local tumor microenvironment to an immunosuppressive state that helps tumor cells evade immunosurveillance. Epacadostat is a potent and specific oral inhibitor of the IDO-1 enzyme that is being evaluated in combination with both pembrolizumab and nivolumab. In an open-label phase I/II study in multiple tumor types (ECHO-202/KEYNOTE-037), epacadostat plus pembrolizumab showed promising antitumor activity in patients with advanced melanoma. In 63 evaluable patients with melanoma, the overall response rate (ORR) was 56% (complete response [CR], 14%), and the disease control rate was 71%. Median progression-free survival (PFS) was 12.4 months, and 18-month PFS was 49%. Among treatment-naive patients with advanced disease treated with 100 mg of epacadostat (38 patients), ORR was 58% (CR, 8%), and the disease control rate was 74%. Epacadostat plus pembrolizumab showed a favorable safety profile, with an incidence of related grade 3/4 toxicity of 20%. This combination is being further evaluated versus pembrolizumab monotherapy in a phase III study of 706 patients with advanced melanoma (ECHO-301/KEYNOTE-252). Similarly, in the open-label phase I/II ECHO-204 study of patients with advanced solid tumors, epacadostat plus nivolumab was generally well tolerated and showed promising activity. In 40 patients with advanced melanoma not previously treated with IDO inhibitors or checkpoint inhibitors, except for anti–CTLA-4 as first-line therapy, ORR was 63% (CR, 5%), and the disease control rate was 88%. Response was observed regardless of PD-L1 expression. Across all tumor types, toxicity was manageable, although treatment-related grade 3 rash and treatment-related adverse events (TRAEs) leading to discontinuation were increased with a higher dose of twice daily epacadostat (300 vs. 100 mg). Another IDO-1 inhibitor, BMS-986205, is also being tested in combination with nivolumab. In a phase I/IIA trial in patients with cervical, bladder, or other advanced cancers (CA017-003), BMS-986205 plus nivolumab showed antitumor activity and had a favorable safety profile in 289 heavily pretreated patients, with grade 3/4 TRAEs in 11% of patients and no treatment-related deaths. A phase III randomized, double-blind study of BMS-986205 plus nivolumab versus nivolumab monotherapy in patients with advanced melanoma has been initiated (NCT03329846).

**Anti–PD-1 plus anti–LAG-3.** As a potentially synergistic immune pathway to PD-1/PD-L1, the anti–LAG-3 gene has emerged as an immune checkpoint receptor that regulates T-cell function. The anti–LAG-3 therapy BMS-986016 is being investigated in combination with nivolumab. In an ongoing expansion study of 48 heavily pretreated patients with advanced melanoma whose disease was refractory to or relapsed on anti–PD-1/PD-L1 therapy, the ORR was 12.5%. Patients with LAG-3 tumor expression greater than or equal to 1% (25 patients) had a nearly threefold improvement in ORR compared with patients with less than 1% LAG-3 expression (14 patients; 20% vs. 7.1%). The safety profile was similar to nivolumab monotherapy.

**Anti–PD-1/anti–CTLA-4 plus HDAC inhibitor.** Entinostat is a selective HDAC inhibitor shown to enhance immune checkpoint inhibitor activity in preclinical studies. In preliminary data, entinostat plus pembrolizumab showed promising activity in patients (13 patients) whose disease was refractory to previous treatment with checkpoint inhibitors. Of note, one patient with a confirmed partial response was converted from PD-L1 negative in a pretreatment tumor biopsy to PD-L1 positive post-treatment. However, in another phase I trial, another HDAC inhibitor, panobinostat, did not seem to increase response when added to standard ipilimumab therapy in patients with advanced melanoma.

**Anti–PD-1/anti–CTLA-4 plus TLR-9 agonist.** TLR-9 induces IFN-α and antigen-presenting cell maturation, resulting in the activation and proliferation of tumor-infiltrating lymphocytes (TILs). Combining intratumoral dendritic cell activation to enhance T-cell priming with checkpoint blockade may be key in patients who are refractory to immunotherapy. In a phase I/II trial, the TLR-9 agonist IMO-2125 was administered intratumorally to patients with PD-1/PD-L1–refractory melanoma in combination with ipilimumab (18 patients) or pembrolizumab (four patients). Dose-limiting toxicities have not been reported. Clinical
benefit has been observed, with biopsies showing maturation of the mDC1 subset (CD1c+, CD303−), upregulation of PD-L1 by malignant cells, and an IFN-α response gene signature. Biopsies of un.injected tumors showed evidence of an abscopal effect, with expression of CD56+ and Ki67+ effector CD8+ T cells in responding patients. A phase II trial is ongoing.

**Anti–PD-1 plus anti-GITR.** GITR is a costimulatory activating receptor that is upregulated on activated T cells and expressed at higher levels in regulatory T cells than effector T cells. BMS-986156 is a fully human IgG1 agonist monoclonal antibody that binds GITR and promotes effector T cell activation with the possible reduction and inactivation of regulatory T cells. In a phase I/IIA study in patients with advanced solid tumors, the combination of BMS-986156 plus nivolumab was well tolerated, with no dose-limiting toxicities and low immunogenicity, whereas antitumor activity was observed at doses expected to be biologically active. Additional evaluation of this combination is ongoing.

**Anti–PD-1 plus pegylated IL-2 (NKTR-214).** NKTR-314 is a CD122-biased immune-stimulatory cytokine that selectively binds to the IL-2 receptor-β. Biased signaling preferentially activates and expands effector T cells and natural killer cells over regulatory T cells and increases proliferation of TILs and PD-1 expression on effector T cells in the tumor microenvironment. In the ongoing phase I/II PIVOT-02 study of NKTR-214 plus nivolumab in patients with selected solid tumors, the ORR was 64% and the disease control rate was 91% in 11 treatment-naive patients with advanced melanoma. The combination was well tolerated, with no study discontinuations because of TRAEs and no treatment-related deaths. In addition, NKTR-214 did not increase the risk for immune-related TRAEs associated with nivolumab.

**Targeted Therapies**

Inhibition of both MEK and CDK4/6 may suppress MAP kinase pathway activation and cell cycle checkpoint dysregulation in NRAS-mutant melanoma, resulting in enhanced antitumor activity. The MEK inhibitor binimetinib plus the CDK4/6 inhibitor ribociclib in combination exhibited favorable efficacy and a manageable safety profile in a phase Ib trial of 16 patients with metastatic NRAS-mutant melanoma. In a phase Ib/II dose-escalation study evaluating triple combination therapy with a BRAF inhibitor (encorafenib) plus binimetinib and ribociclib in patients with high tumor burden, BRAF V600-mutant solid tumors, and melanoma, more than one-half of patients had reductions in tumor size. However, the median PFS with triple combination therapy was less than that previously observed with the dual combination of encorafenib plus binimetinib (9.2 vs. 11.3 months). Moreover, the addition of ribociclib seemed to increase toxicity compared with the dual combination, with elevated transaminases the most frequent reason for discontinuation, consistent with the known tolerability profile of ribociclib.

**Targeted Therapy Plus Immunotherapy**

Clinical trials to assess the combination of targeted BRAF/MEK inhibitors with immunotherapy are also being conducted. A phase I study (NCT02027961) showed that 3 or 10 mg/kg of the PD-L1 inhibitor intravenous durvalumab every 2 weeks in combination with a BRAF inhibitor (dabrafenib) and MEK inhibitor (trametinib) had a manageable safety profile and evidence of clinical activity in patients with stage IIIIC/IV melanoma. Patients with a BRAF mutation treated with a combination of BRAF and MEK inhibition exhibited the greatest immune activation as well as the greatest clinical activity.

Another ongoing phase I study is KEYNOTE-022, which is investigating the safety and efficacy of pembrolizumab combined with dabrafenib and trametinib in patients with advanced BRAF-mutant melanoma. Fifteen patients were treated with pembrolizumab at 2 mg/kg every 3 weeks and 150 mg of dabrafenib twice daily with 2 mg of trametinib daily. Dose-limiting toxicities were reported in three patients; one patient had grade 4 neutropenia, a second had grade 4 increased alanine aminotransferase, and a third had grade 3 increased aspartate transaminase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (γGT); all discontinued treatment. All events resolved, and no treatment-related deaths were observed. Eleven patients (73%) had grade 3 to 4 TRAEs, and four (27%) discontinued triplet combination treatment. No late or unexpected toxicities occurred with longer follow-up. Confirmed ORR was 67% (10 of 15 patients) with 13% of CR (2 of 15 patients). Seven of 11 patients with a response have not progressed with median follow-up of approximately 20 months. Part 3 of KEYNOTE-022 is a double-blind study of pembrolizumab plus dabrafenib plus trametinib versus placebo plus dabrafenib plus trametinib. In another phase III trial, dabrafenib plus trametinib is being evaluated in metastatic BRAF-mutant melanoma in combination with and without the PD-1 inhibitor, PDR001 (NCT02967692).

Another triplet combination being assessed in patients with metastatic BRAF-mutant melanoma is the anti–PD-L1 inhibitor atezolizumab in combination with the BRAF inhibitor vemurafenib plus the MEK inhibitor cobimetinib. In a phase IB dose escalation and expansion cohort study, patients received a 28-day lead in of cobimetinib plus vemurafenib followed by triple combination of 720 mg of vemurafenib, 60 mg of cobimetinib, and 800 mg of atezolizumab. Preliminary data from 34 patients suggest that this triple combination has a manageable safety profile, with adverse events similar to those observed with atezolizumab plus vemurafenib, and promising antitumor activity in patients with BRAF V600–mutant metastatic melanoma. The phase III TRILOGY trial (NCT02908672) evaluating atezolizumab plus cobimetinib plus vemurafenib versus placebo plus cobimetinib plus vemurafenib in untreated BRAFv600-mutant metastatic or unresectable locally advanced melanoma is underway.

The combination of atezolizumab and cobimetinib has also been investigated in patients with BRAF wild type. A
phase IB study in solid tumors included 20 patients with metastatic melanoma, 10 of whom had BRAF wild-type tumors.22 A clinical benefit of the combination was observed regardless of BRAF status (BRAF-mutant: ORR, 40%; median PFS, 11.9 months; BRAF wild type: ORR, 50%; median PFS, 15.7 months). Atezolizumab and cobimetinib also had a manageable safety profile, similar to that observed with atezolizumab alone or cobimetinib plus vemurafenib. A phase III trial of atezolizumab plus cobimetinib versus pembrolizumab is underway in patients with treatment-naive, BRAF-mutant, or BRAF wild-type metastatic melanoma (NCT03273153).

**NOVEL TARGETS**

In the years since large-scale genomic analyses have been conducted in melanoma, MAP kinase pathway activation via BRAF, NRAS, and NF1 mutations has become considered a hallmark of this disease.23 Approximately 85% of advance melanomas harbor at least one of these genetic alterations. Beyond KIT and GNAQ/GNA11 mutations in 1% subpopulations, it remains unclear what activated oncopgenes drive the remaining fraction of melanomas, although it is known that many of these tumors harbor few somatic alterations and that some are associated with gene fusions that may constitute their driver oncopgenes. By far, the greatest therapeutic inroads with molecularly targeted therapy in melanoma have been made in the BRAF-mutant population and specifically, those that harbor BRAF V600 mutations. BRAF/MEK combination therapy induces tumor regression and decreased fluorodeoxyglucose uptake in nearly all patients.24 De novo and acquired resistance to BRAF/MEK therapy has been the focus of extensive research over the past several years, yielding insights into potential new therapeutic targets. The currently available BRAF inhibitors are unable to block MAP kinase pathway signaling in cells that harbor non-V600 BRAF mutations, BRAF fusions, or NRAS or NF1 mutations. In fact, these agents have an MAP kinase pathway stimulatory effect.25,26 MEK inhibitors are able to block the MAP kinase pathway in preclinical models of these genetic subtypes. However, in clinical trials, the therapeutic index of MEK inhibitor monotherapy is limited by MAP kinase pathway inhibition in normal tissue, able to achieve objective responses in approximately 15% of patients and tumor regression of any degree in 60%.27 Although many of these tumors harbor few somatic alterations and that some are associated with gene fusions that may constitute their driver oncopgenes. By far, the greatest therapeutic inroads with molecularly targeted therapy in melanoma have been made in the BRAF-mutant population and specifically, those that harbor BRAF V600 mutations. BRAF/MEK combination therapy induces tumor regression and decreased fluorodeoxyglucose uptake in nearly all patients.24 De novo and acquired resistance to BRAF/MEK therapy has been the focus of extensive research over the past several years, yielding insights into potential new therapeutic targets. The currently available BRAF inhibitors are unable to block MAP kinase pathway signaling in cells that harbor non-V600 BRAF mutations, BRAF fusions, or NRAS or NF1 mutations. In fact, these agents have an MAP kinase pathway stimulatory effect.25,26 MEK inhibitors are able to block the MAP kinase pathway in preclinical models of these genetic subtypes. However, in clinical trials, the therapeutic index of MEK inhibitor monotherapy is limited by MAP kinase pathway inhibition in normal tissue, able to achieve objective responses in approximately 15% of patients and tumor regression of any degree in 60%.27 Although many of the new therapeutic targets being considered to overcome BRAF/MEK inhibitor therapy also seem relevant for melanomas harboring non-V600 BRAF mutations, BRAF fusions, or NRAS or NF1 mutations, the reality is that MEK inhibitor monotherapy places far less selective pressure on these tumors than BRAF/MEK inhibition does in BRAF V600–mutant melanoma.

In preclinical models, there is no clear plateau in the dose-response relationship between MAP kinase pathway inhibition and induction of cell death.28 In patients, BRAF/MEK inhibitor combination therapy and MEK inhibitor monotherapy are given very close to their maximum tolerated doses and therefore, leave little room for further optimizing pathway inhibition. It has been hypothesized that inhibitors of downstream components in the MAP kinase pathway might render more complete pathway inhibition and improved efficacy compared with MEK inhibitors. Most attention has been focused on ERK inhibitors, of which several have entered clinical trials. Preclinically, ERK inhibitors have broader efficacy in melanoma cell line panels than MEK inhibitors.29 Phase I/II evidence is now available for one ERK inhibitor, ulixertinib (BVD-523).30 Although a relatively small number of patients with melanoma have been treated to date, this agent has produced objective responses in patients with BRAF/MEK inhibitor–refractory and –targeted therapy-naïve NRAS mutant. This encouraging activity supports additional development, with the BRAF/ERK combination being perhaps the most relevant strategy for the BRAF V600–mutant population and ERK-based combination strategies for the other MAP kinase pathway–activated subsets. RSK is directly activated by ERK and has also emerged as a potential therapeutic target based on recent studies indicating that selective RSK inhibition can overcome BRAF/MEK resistance in preclinical models.31,32 Clinically relevant RSK inhibitors have not yet been developed.

An extensive literature supports the role of PI3 kinase pathway signaling in both de novo and acquired resistance to MAP kinase pathway inhibition in melanoma. However, as has been true in other cancer contexts, it has proven challenging to identify the exact components within the pathway that are critical for mediating therapeutic resistance and can be safely targeted in normal tissue. Many inhibitors of class I PI3 kinases, Akt, and mTOR have been introduced into clinical trials and in combination with BRAF and MEK inhibitors. None of these combinations have produced clinical benefit that matches the promise suggested by preclinical studies. Although there are some melanomas that activate PI3 kinase pathway signaling through intrinsic alterations in the pathway (PTEN loss in about 20% of melanomas and rare PI3K-activating mutations), activation of the pathway in most cases seems to be a consequence of upregulated expression of several receptor tyrosine kinases or RAS activation.33,34 It seems that coordinated upregulation of multiple receptor tyrosine kinases in individual tumor cells is more common than selective upregulation, making direct targeting of any one receptor unlikely to overcome MAP kinase pathway inhibitor resistance.35 Nonetheless, among the most consistently upregulated receptor tyrosine kinases is AXL. Small molecule and monoclonal antibody inhibitors of AXL have been proposed for development in melanoma, but again, they will likely have limited impact if compensatory signaling can be mediated by other receptor tyrosine kinases. An intriguing approach that is currently being pursued is the development of antibody-drug conjugates to deliver a chemotherapy payload with an AXL-directed antibody (NCT02988817). Given the historical refractoriness to conventional cytotoxic chemotherapy in melanoma and the stem cell–like properties that have been ascribed to MITF-low/AXL-high MAP kinase pathway–resistant melanomas, the clinical benefits of this approach may be somewhat limited.
Signaling molecules downstream of PI3K, Akt, and mTOR have recently been the subject of preclinical investigation and may yield new promising therapeutic targets. S6 kinase, which is regulated by mTOR, has been shown to be inhibited by BRAF inhibition in cells that undergo apoptosis, whereas its activation persists in resistant cells. Gene silencing approaches and now relatively selective inhibitors seem to overcome resistance. S6K inhibitors have not yet been introduced clinically, and therefore, their safety alone or in combination is not yet known. S6K regulates the expression of translational elongation factors in preclinical evidence that has suggested eIF4F and eIF4E as being particularly critical in meeting the S6 kinase–dependent resistance mechanism. This evidence has also been generated using gene silencing approaches and preclinical tool compounds, making it difficult to ascertain the potential safety of this approach.

The PI3K pathway is also well known to regulate cellular metabolism, leading to interest in directly targeting those processes. Several preclinical studies and analyses of BRAF/MEK-resistant tumor samples have identified the switch from glycolysis to oxidative phosphorylation early after initiation of these inhibitors. The cancer metabolism field is still relatively immature with regard to enumeration of specific therapeutic targets that would have preferential toxicity for cancer cells over the many normal cells that similarly rely on oxidative phosphorylation. Nonetheless, preclinical studies with the AMP kinase activator and mitochondrial respiration complex chain complex I protein, phenformin, show synergy in vitro and in vivo without overt evidence of toxicity in mouse models. The fact that phenformin was a widely used drug for diabetes before its removal from the market because of a 1% rate of lactic acidosis would seem to indicate that this agent could be redeployed as a cancer therapeutic. An ongoing phase I trial in combination with BRAF/MEK inhibition (NCT03026517) must determine whether similar doses used in the management of diabetes are sufficient to render the desired metabolic effect to overcome therapeutic resistance. An intriguing new metabolism target has emerged from other studies that have centered on the HSP90 isoform that is selectively expressed in mitochondria. Gamitrinib is an inhibitor of this heat shock protein and shows broad ability to overcome BRAF inhibitor resistance in cell lines as well as a small number of in vivo models evaluated to date.

An increasing body of evidence indicates that the surviving cell population after the initial weeks of BRAF/MEK inhibitor therapy undergoes an epigenetic-mediated state change. This is reflected by altered expression of transcription factors critical to the melanocyte lineage, and it is most commonly referred to as the MITF low state. In melanoma cell lines exposed to BRAF inhibitors, altered gene transcription associated with this state is reversible on drug withdrawal. It is hypothesized that the emerging class of novel inhibitors of key epigenetic regulators may impede the transition of MITF high cells to the MITF flow state. In the published literature, only BRD4 inhibition has been described as an approach capable of overcoming this form of therapeutic resistance. However, with many new agents in this class emerging, there is broad interest in exploring the ability of these agents to block this process and maintain cells in the MAP kinase pathway–sensitive state.

ADOPTIVE CELL THERAPY
Before the development of monoclonal antibodies inhibiting checkpoint blockade, the initial evidence that manipulation of the host immune system could result in tumor regression was provided by successful trials of IL-2, a T-cell growth factor, in treating patients with metastatic melanoma and renal cell cancer. This nonspecific stimulation of the entire lymphocyte repertoire produced rare but durable results, with a CR rate of 4% in patients with metastatic melanoma. At a time when the only U.S. Food and Drug Administration–approved medication for metastatic melanoma was dacarbazine, a relatively ineffective chemotherapy, a high-dose regimen of IL-2 was approved in 1998. However, the toxicities associated with administration, such as capillary leak syndrome, necessitated inpatient treatment, and the therapy was never widely adopted.

To better understand the mechanism of this immune-mediated phenomenon, early murine research suggested that natural killer cells and lymphokine-activated killer cells could mediate tumor regression, but a randomized human clinical trial of IL-2 with and without lymphokine activated killer cells showed no difference in response rate. However, lymphocytes cultured from fragments of resected tumors (TILs) were more potent than lymphokine-activated killer cells in murine models of melanoma metastasis. TILs are generated by the sterile processing of a freshly resected tumor deposit. Although techniques vary from institution to institution, usually small fragments (approximately 2–3 mm³) are placed in culture with media supplemented with high-dose IL-2. Common variations include combining multiple fragments in culture, creating an enzymatic tumor digest rather than sharp dissection into fragments, or supplementing media with different cytokine cocktails. TILs are nonadherent and harvested from media over the course of 2 to 3 weeks.

The first human experience of adoptive cell therapy with TILs was performed in the Surgery Branch of the National Cancer Institute and included 20 patients with metastatic melanoma. The regimen consisted of a single dose of cyclophosphamide, intravenous infusion of autologous TILs, and high-dose IL-2; objective responses were seen in 11 of 20 (55%) patients, including one CR. Toxicities were transient, similar to IL-2 administration alone, and did not result in treatment-related mortalities. The responses, however, were largely of short duration.

Sequential changes were made in an attempt to improve the response rate. Most importantly, the preparative chemotherapy regimen was enhanced to provide deeper lymphodepletion without myelosuppression. The combination of cyclophosphamide and fludarabine conditioned each patient’s immune milieu, providing the administered cells
an IL-7– and IL-15–rich cytokine environment to promote lymphocyte expansion. When this nonmyeloablative regimen was added, the CR rate rose to 12%. Additional trials added different doses of total body irradiation (2 or 12 Gy), similar to transplant-style conditioning, to strengthen the lymphodepletion, and although sequential single-arm studies were promising, a randomized trial showed no improvement in CR rates over nonmyeloablative conditioning alone, with a 24% CR rate in each arm.

Other groups have made valuable contributions to the development of autologous TIL transfer for metastatic melanoma, showing that tumor regression is possible using different growth conditions, with different culture selection criteria, using different T-cell subsets, and with administration of low-dose IL-2 after cell transfer. However, the complexity of this strategy compared with checkpoint blockade inhibition has called into question its viability as a potential treatment of patients with metastatic melanoma.

One remarkable aspect of adoptive cell transfer to consider is the depth and durability of response. In 194 patients treated in four different trials at the Surgery Branch, there have been 46 patients with CRs. Only two have recurred, with median potential follow-up of over 6 years. The median survival of the entire cohort is just over 2 years (24.5 months), with 5- and 10-year survival rates greater than 30% (S. Rosenberg, unpublished data). In those who have progressed after partial responses, surgical resection of progressing lesions in carefully selected patients can also provide secondary long-term disease control, with a 5-year postoperative survival rate of 57%. These data together suggest that the strategy may be capable of eliminating micrometastatic disease, even when unable to eradicate radiologically evident tumors.

Because checkpoint blockade inhibition has become the standard first-line therapy for patients with metastatic melanoma, the clinical equipoise no longer exists to test the strategies head to head in a randomized fashion, and any potential future role for adoptive cell transfer likely exists after monoclonal antibody therapy has failed to control disease. Questions then arise as to the effectiveness of adoptive cell transfer in a population of patients whose immune systems have already been challenged to engage tumor in a nonspecific fashion.

The historical studies of adoptive cell transfer with autologous TIL were performed before the U.S. Food and Drug Administration approval of the checkpoint blockade inhibitors. The most recently published adoptive cell transfer trial accrued patients from 2011 to 2013, bridging the introduction of these antibodies to the wider oncology community. Approximately 40% of patients had progressed through anti–CTLA-4 therapy, and compared with the cohort as a whole, Objective response rates were nearly identical (ORR, 55%; CR, 26%). There were too few patients to provide meaningful analysis on response rates after progression to anti–PD-1/PD-L1 agents.

It is reasonable to predict that response rates after unsuccessful manipulation of the PD-1/PD-L1 axis may be lower. Unlike CTLA-4, the role of PD-1/PD-L1 is to modulate immune responses in peripheral tissues, minimizing inflammation after antigen recognition by effector T cells. TILs generated from tumors that have not responded to checkpoint blockade inhibition may be qualitatively or quantitatively different. In a small sample of patients undergoing serial biopsy, patients who were not responsive had lower CD8+ T-cell density at all time points. It is possible that intratumoral T-cell diversity is also affected by anti–PD-1 treatment but by different parameters in patients with and without exposure to anti–CTLA-4.

In currently accruing trials of adoptive cell transfer with TIL in patients after PD-1 progression, preliminary data suggest an ORR of less than 25%. Although lower than responses in patients who are PD-1 naïve, the ability to mediate tumor regression in this patient population suggests that a component of the adoptive transfer strategy can overcome a tumor’s resistance to immunotherapy: lymphodepletion may alter the tumor microenvironment, the process of generating TILs may expand rare tumor-reactive clonotypes in vitro, or the bolus delivery of activated T cells may engage different cytolytic mechanisms than checkpoint inhibition.

Future development of adoptive cell transfer with TILs for melanoma will likely focus on its potential role as a post-checkpoint salvage therapy. The single-treatment strategy can mediate durable regression in patients whose tumors are refractory to approved medications. Ongoing research may include attempts to generate TILs from patients before the start of anti–PD-1/PD-L1 antibodies, combining adoptive cell transfer with checkpoint blockade (NCT02621021), using gene-editing techniques to manipulate T-cell differentiation, or investigating TIL cultures for reactivity to potential neoantigens to enable selection of an enhanced tumor-reactive infusion product.

CONCLUSION

Major advances in the systemic therapy of melanoma have been achieved over recent years. However, additional improvements are still required, and several emerging strategies are becoming apparent. Combined immunotherapies (iplimitumab with nivolumab) and combined BRAF and MEK inhibition (dabrafenib with trametinib and vemurafenib with cobimetinib) were the first combinations of the recent wave of new agents to show additional benefit in overall survival in melanoma beyond what has been achieved with monotherapy. The next step will be the further investigation of several new immunotherapy and/or targeted therapy combinations. The identification of novel therapeutic targets in the MAP kinase pathway also offers opportunities to improve outcomes by overcoming de novo and acquired resistance to BRAF/MEK inhibition. Finally, adoptive cell transfer may have a potential role in patients whose disease has progressed after treatment with checkpoint inhibitors. Overall, these new approaches offer further potential to improve long-term outcomes for patients with advanced melanoma.
References


Practice-Changing Developments in Stage III Melanoma: Surgery, Adjuvant Targeted Therapy, and Immunotherapy

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OVERVIEW

In this article, we will focus on the practice-changing developments for stage III melanoma, from the use of the sentinel node (SN) biopsy to complete lymph node dissection (CLND) and upcoming adjuvant therapies. MSLT-1 (Multicenter Selective Lymphadenectomy Trial-1) was the first and only prospective randomized controlled trial to examine whether the SN biopsy has any notable melanoma-specific survival benefit (primary endpoint). MSLT-1 randomly assigned 2,001 patients to undergo either wide local excision (WLE) and an SN biopsy or WLE and nodal observation. Two prospective randomized controlled trials have examined the potential benefit for immediate CLND versus delayed CLND after sequential observation. Both the DECOG-SLT and MSLT-2 trials failed to demonstrate a notable benefit for immediate CLND; therefore, sequential follow-up with ultrasonography and a delayed CLND in the case of relapse should be considered the new standard of care. The CheckMate 238 study demonstrated a notable benefit for adjuvant nivolumab in terms of 18-month relapse-free survival (RFS) rates compared with high-dose adjuvant ipilimumab. Single-agent adjuvant BRAF inhibition has been examined and failed to improve RFS. However, the COMBI-AD study did demonstrate a substantial benefit for combination BRAF and MEK inhibition for patients with BRAF-mutated resected stage IIIA to IIIC melanoma.

A duvant nivolumab is superior to adjuvant high-dose ipilimumab in terms of a potential reduction in relapses and is also much better tolerated because of a notably better toxicity profile. Treatment of regional lymph node metastases has undergone substantial changes since the first prospective randomized controlled trials (RCTs) examining elective lymph node dissection were reported in the 1970s. Four RCTs were negative for the entire population with respect to a survival benefit for elective lymph node dissection, but two studies indicated a potential benefit for the node-positive subgroup and for intermediate-thickness melanomas.

SURGERY

Simultaneous to these RCTs, Morton et al developed lymphatic mapping as a technique for the SN biopsy in melanoma. This led to the hypothesis that with the use of the SN biopsy, the correct subgroup of node-positive patients with intermediate-thickness melanoma could be targeted for early lymph node dissection and thereby potentially improve their survival.

MSLT-1 was the first and only prospective RCT to examine whether the SN biopsy has any notable melanoma-specific survival benefit (primary endpoint). MSLT-1 randomly assigned 2,001 patients to undergo either WLE and an SN biopsy or WLE and nodal observation. Both the interim and final results were negative, with 10-year melanoma-specific survival rates of 81.4% for the SN biopsy group versus 78.3% for the nodal observation group (p = .18).

Despite these findings, the authors concluded that biopsy-based management of intermediate-thickness melanomas improves melanoma-specific survival for patients with nodal metastases. This was based on a subgroup analysis, which did not take into account any false-negative and/or positive SN biopsy results. Moreover, the authors used an unconventional new statistical technique, the accelerated-failure-time latent subgroup analysis. There was inherent bias in this method, because it was developed by the same MSLT-1 statistician on the interim data of the same study and was not validated outside of MSLT-1. Therefore, we must conclude that there is no unequivocally proven survival benefit for undergoing an SN biopsy.

Despite the absence of survival benefit, the SN biopsy should still be considered as standard of care staging for intermediate-thickness/thick melanomas, because it has important consequences for adjuvant therapy decisions. Moreover, SN tumor burden measured as the diameter of the largest lesion is the most reproducible prognostic factor and can be used to further refine which subgroups need adjuvant therapy and which do not.
Immediate CLND for a positive SN biopsy has been studied in two prospective RCTs. First, the DECOG-SLT study by Leiter et al17 reported no distant metastasis-free survival difference for CLND compared with sequential ultrasound follow-up at 3 years (77% vs. 74.9%, respectively). Second, the larger MSLT-2 study showed the same results with respect to 3-year melanoma-specific survival (86% vs. 86%; p = .42).18 CLND does (initially) give a slightly better “in-field” control and the additional pathology staging might provide more information to adequately stage patients for adjuvant therapy (studies). However, Madu et al19 demonstrated that, based on the primary and SN tumor burden information alone, the additional staging information of a CLND was only 6%. Given the small amount of additional information from the CLND along with the lack of survival benefit and the potential complications of CLND, the authors concluded that the risk did not out way the benefits. Therefore, routine immediate CLND should not be routinely used, as suggested by Coit20 and a delayed CLND should be used in the case of immediate CLND should not be routinely used, as suggested that the risk did not outweigh the benefits. Therefore, routine immediate CLND should not be routinely used, as suggested by Coit20 and a delayed CLND should be used in the case of an isolated regional recurrence in due time. However, the risks and benefits of a CLND should be carefully reviewed with all patients who have a positive SLN. However, all patients who have macroscopic (palpable) disease in the lymph node should still undergo an immediate complete lymph node dissection.

FORMER ADJUVANT THERAPY

Patients with stage IIB/C and stage III melanoma, despite radical surgery, have a high risk for relapse within 5 years of their initial treatment. Historically, interferon-alpha-2B has been investigated in different schedules as a potential adjuvant therapy for melanoma. A meta-analysis of 14 RCTs with more than 8,000 patients demonstrated a notable effect of interferon-alpha-2B on RFS but not or only very limitedly in specific subgroups on overall survival.21 Based on these data and factoring in the toxicity of interferon-alpha-2B, this therapeutic option has not been accepted as standard of care worldwide and is now rendered obsolete with the new therapies were available for adjuvant treatment of stage III melanoma.

ADJUVANT TARGETED THERAPY

BRIM-8 and COMBI-AD are the first two studies on adjuvant targeted therapy for BRAF-mutated melanoma. The BRIM-8 study compared adjuvant vemurafenib versus placebo and failed to show a substantial improvement in the primary endpoint of RFS.34 However, this may have been a result of the selected study population because it included patients with disease stages ranging from lower-risk stage II through stage IIIC. In stage II, the numbers needed to treat to rescue one relapse from occurring are much higher than in stage IIIC because the risk of relapse is much lower in stage II, thus requiring a much larger sample size to demonstrate any potential notable benefit. In addition, the study used single-agent BRAF inhibition and did not use what is now the standard of care in stage IV disease, which is a combination of BRAF/MEK inhibitors. This is especially true for patients with high-risk stage IIIC disease, who actually mimic the survival curves of stage IV disease, but with a delay of a few months (i.e., very often, these patients already have microscopically undetectable stage IV disease at the time they receive treatment for stage IIIC disease).

The COMBI-AD study compared adjuvant combination dabrafenib/trametinib with a double placebo in stage IIIA (> 1 mm SN tumor burden12-15), stage IIIB, and stage IIIC melanoma.35 After a median follow-up of 2.8 years, the estimated 3-year RFS rates were 58% in the combination therapy group versus 39% in the placebo groups (p < .001).35 The first exploratory interim analysis of overall survival also showed a survival benefit for the combination therapy group at 3 years (86% vs. 77%), although it was not statistically significant.35 Adjuvant combination dabrafenib/trametinib should therefore be considered as a viable adjuvant therapy option for patients with stage III melanoma harboring the BRAF V600 mutation.

ADJUVANT IMMUNOTHERAPY

EORTC 18071 was the first adjuvant study with immune checkpoint blockade, which examined adjuvant high-dose ipilimumab (10 mg/kg) versus placebo in resected stage IIIA (> 1 mm SN tumor burden12-15), stage IIIB, and stage IIIC melanoma. EORTC 18071 is the most mature study with the current treatments and showed a clear benefit in terms of 5-year RFS, distant metastasis-free survival, and improvement in overall survival.36 However, because of the high rate of severe (grade 3/4 and even 1% grade 5) toxicity, this treatment will likely not be considered as a viable adjuvant therapy option considering other developments of more effective and less toxic adjuvant treatments.

Investigators recently reported the first primary endpoint analysis of the CheckMate 238 study. This study examined adjuvant nivolumab versus adjuvant high-dose ipilimumab in resected stage IIIB, stage IIIC, and stage IV disease. At a minimum follow-up of 18 months, 1-year RFS rates were

PRACTICAL APPLICATIONS

- There is no unequivocal evidence for survival benefit of an SN procedure; nevertheless, it should be considered as standard of care staging.
- Immediate CLND does not improve survival compared with delayed CLND after sequential ultrasound observation for a positive SN biopsy.
- Single-agent adjuvant BRAF inhibition is not sufficiently effective in reducing the risk for relapse in stage III melanoma.
- Combined adjuvant BRAF and MEK inhibition does reduce the risk of relapse in stage III melanoma.
70.5% for nivolumab versus 60.8% for high-dose ipilimumab (p < .001). Moreover, nivolumab was much better tolerated, with 14.4% grade 3/4 adverse events compared with 45.9% in the high-dose ipilimumab group. A recent press release reported that adjuvant pembrolizumab compared with placebo for resected stage IIIA (> 1 mm SN tumor burden), stage IIIB, and stage IIIC melanoma also leads to a notable improvement in RFS (data to be presented at the American Association for Cancer Research 2018 Annual Meeting).

Thus, adjuvant anti–PD-1 should be considered the new standard of care for patients with BRAF wild-type melanoma. For BRAF-mutated melanoma, both adjuvant anti–PD-1 and dabrafenib/trametinib should currently be considered as potential options, although there is currently no comparator study.

How to treat patients with stage IIB, stage IIC, and stage IIIA melanoma in the adjuvant setting is an area of controversy. Although there are some albeit limited data on this group in the BRAF/MEK inhibitor trials, patients with stage II disease were not included in the immunotherapy trials. In addition, the CheckMate 238 study did not include patients with stage IIIA disease, whereas the EORTC 1325/KEYNOTE 054 trial did. A study requirement was that there should be sufficient material to allow for PD-L1 testing, which can be problematic for patients with stage IIIA disease after diagnostic pathology of their SN; there might be limited residual material, which would exclude the patient from the study. Given the likely limited number of patients with stage IIIA disease on this study, it is difficult to determine the benefit of immunotherapy in this population.

More data on whether the risk of immunotherapy targeted therapy is worth the potential benefit in this population of patients is necessary, because surgery alone already cures the majority of patients with lower-stage disease. Additional studies are also needed to explore whether these therapies offer an advantage in the adjuvant setting versus treatment upon relapse.

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PATIENT AND SURVIVOR CARE
Cardiac imaging with echocardiography should be considered in the follow-up period in all survivors at high risk for cardiomyopathy. For the last 4 decades, oncologists have been aware that some cancer treatments, particularly chemotherapeutic agents and radiation, can result in cardiovascular complications, such as ischemic cardiovascular disease, cardiomyopathy, clinical heart failure, and arrhythmias. Although treatments options for patients with cancer have evolved with the introduction of new targeted therapies, there continues to be a growing appreciation of the cardiac toxicities of cancer therapies—thus the emergence of a new field of “cardio-oncology.”1-3 In parallel, there has been a rapid growth in the biologic understanding of cancer, molecular pathways, genetic susceptibility to cancer, and cancer syndromes as well as the toxicities of these therapies.4 Here, we present an overview of the development of cardio-oncology, the cardiac toxicity of new anticancer agents, and newer techniques, such as imaging and biomarkers, that can be used for the monitoring and prevention of cardiac complications of anticancer therapies.

CARDIAC TOXICITIES IN THE ERA OF PRECISION MEDICINE
Overview of Cardiovascular Toxicities of Current Anticancer Therapies
A number of chemotherapeutic agents can cause cardiomyopathy and heart failure (Table 1). Perhaps best studied are the anthracyclines. First described in the 1970s by Lefrak and colleagues,5 the incidence of anthracycline-induced congestive heart failure is dose dependent, with an estimated 2% at 200 mg/m², 5% at 400 mg/m², 16% at 500 mg/m², and 26% at 550 mg/m².5 Other risk factors include female sex and extremes of age (affecting both younger and older patients).6 For those over the age of 65, there is a twofold increased risk of doxorubicin-induced congestive heart failure compared with in those younger than 65 when adjusting for a history of low/normal ejection fraction, gender, history of cardiac disease, and performance status.7 Similarly, in the Children’s Oncology Group, the young seem particularly at risk for cardiac toxicity; childhood cancer survivors are at a 15-fold higher risk of cardiomyopathy compared with age-matched controls.8-10 The dose-dependent relationship of anthracyclines and heart failure in this patient population has also been well established, with an additional rising increase in those who also received chest radiation.9 Some literature suggest that liposomal formulation may result in less cardiac toxicity. Skubitz et al11 documented a case series in which individuals received more than 800 mg/m² without any evidence of cardiac dysfunction. In ovarian cancer trials, it also seems that doses up to 550 mg/m² are safe from a cardiac perspective.12 When administered at modified doses of 45 mg/m² every 4 weeks, no cardiac toxicity has been observed.13

More recently, researchers have tried to identify particular genetic variants that could modify cardiomyopathy risk.14-17 Genome-wide association studies have been conducted in...
childhood cancer survivors with and without cardiomyopathy (cases and controls, respectively) to identify whether individuals with single-nucleotide polymorphism in carnitine, remodeling, and alcohol reduction pathways are predisposed to developing anthracycline cardiac toxicity. For those exposed to a high dose of anthracycline, the rs1786814 GG genotype (on the CEF4 gene) conferred a 10.2-fold risk of cardiomyopathy compared with a GA/AA genotype.16 The re2232228 AA genotype in the hyaluronan synthase 3 gene conferred an 8.9-fold increased risk in cardiomyopathy compared with the GG genotype.15 Subsequent models also suggest that particular single-nucleotide polymorphisms are associated with cardiomyopathy, even in the setting of low-dose anthracyclines. Carbonyl reductases catalyze reduction of anthracines to cardiotoxic alcohol metabolites. For those with a polymorphism having the CBR3 V244M homozygous G genotype, exposure to low-dose anthracyclines at doses of 101–150 mg/m² had increased rates of anthracycline cardiomyopathy.14 In one study of hematopoietic stem cell transplant recipients, a combined clinical and genetic evaluation compared with a purely clinical model.19

Cardiac Toxicities in Cancer Survivors

Although many patients are at risk for developing acute cardiac toxicities during cancer therapies, it has become clear that both childhood cancer survivors and survivors of hematopoietic stem cell transplantation have long-term cardiac risk.19-21 Although often related to anthracyclines and radiation, many survivors have an increase in the number of cardiovascular events but also, a reduction in new lung cancers (although the latter was not a predefined endpoint).40,41 In the results of the CANTOS trial, an inhibitor of interleukin-1B (IL-1B), a proinflammatory, showed reductions in cardiac events but also, a reduction in new lung cancers (although the latter was not a predefined endpoint).40,41

More recently, another risk factor, clonal hematopoiesis, has emerged as a risk factor for hematologic malignancies and atherosclerosis.42-45 Human aging, known to be a risk factor for both cancer and cardiovascular disease, is associated with an increase in the frequency of somatic mutations in hematopoietic cells,45 including the epigenetic modifier enzyme Tet methylcytosine dioxygenase-2 (TET2),46 an enzyme known to remove methyl groups from the DNA base cytosine. These somatic mutations and TET2 deficiency have a strong association with the development of blood cancers; they, however, are also associated with an increase in heart attacks and strokes. Fuster and colleagues43 used a mouse model to study TET2 deficiency in atherosclerosis-prone mice. Reconstitution with TET2-deficient cells resulted in a marked increase in atherosclerotic plaque size, suggesting that TET2 mutations in blood cells play a causal role in atherosclerosis.

New Emerging Therapies and Associated Cardiotoxicity

Better delineation of the molecular pathways responsible for tumorigenesis has led to targeting these pathways for more effective treatment. For example, the observation that kinases can become inappropriately active in many cancer types has led to the development of kinases inhibitors for cancer treatment.46 For example, about 20% to 30% of breast cancers overexpress HER2, a kinase receptor; trastuzumab, an antibody targeting HER2, has been effective.

PRACTICAL APPLICATIONS

- There is an increasing amount of evidence of overlapping risk factors between cancer and cardiovascular disease.
- Cardiac risk factors should be assessed in all patients with cancer before starting cancer therapies, during cancer treatment, and in the follow-up survivorship period.
- Cancer therapies can cause a variety of cardiovascular and cardiometabolic complications, including ischemia, cardiomyopathy, heart failure, QT prolongation, vascular disease, and hypertension.
- Cardiac biomarkers may be useful in risk stratifying patients at high risk for cardiac toxicity from cancer therapies.
### TABLE 1. Cancer Therapies and Their Associated Cardiovascular Toxicities

<table>
<thead>
<tr>
<th>Class and Representative</th>
<th>Cellular Target</th>
<th>Common Cardiovascular Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Traditional Cancer Therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiation</td>
<td>N/A</td>
<td>Myocardial ischemia</td>
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<tr>
<td></td>
<td></td>
<td>Pericarditis</td>
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<td></td>
<td></td>
<td>Myocarditis</td>
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<tr>
<td></td>
<td></td>
<td>Valvular heart disease</td>
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<td></td>
<td></td>
<td>Arrhythmia</td>
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<tr>
<td>Anthracyclines</td>
<td></td>
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<tr>
<td>Doxorubicin</td>
<td>Topoisomerase II</td>
<td>Cardiomyopathy (chronic) arrhythmia, cardiomyopathy, myocarditis/pericarditis (acute)</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>DNA and RNA synthesis</td>
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<tr>
<td>Idarubicin</td>
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<td>Epirubicin</td>
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<td>Mitoxantrone</td>
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<tr>
<td>Platinum</td>
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<tr>
<td>Cisplatin</td>
<td>DNA (cross-link DNA)</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Carboplatin</td>
<td></td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Oxaliplatin</td>
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<tr>
<td>Antimetabolites</td>
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<tr>
<td>5-fluorouracil</td>
<td>Thymidylate synthase</td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Thymidylate synthase</td>
<td>Myocardial ischemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmias</td>
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<tr>
<td>Alkylating agents</td>
<td></td>
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<tr>
<td>Cyclophosphamide</td>
<td>DNA (cross-link DNA)</td>
<td>Congestive heart failure</td>
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<td></td>
<td></td>
<td>Myocarditis</td>
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<tr>
<td></td>
<td></td>
<td>Pericarditis</td>
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<tr>
<td>Antimicrotubule agents</td>
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<tr>
<td>Paclitaxel</td>
<td>Microtubule</td>
<td>Arrhythmias (including bradycardia, heart block, premature ventricular contractions, and ventricular tachycardia)</td>
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<td></td>
<td></td>
<td>Thrombosis</td>
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<tr>
<td>Vinca alkaloids</td>
<td>Microtubule</td>
<td>Myocardial ischemia</td>
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<td></td>
<td></td>
<td>Coronary spasm</td>
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<tr>
<td><strong>Novel Targeted Cancer Therapies</strong></td>
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<tr>
<td>HER2 inhibitors</td>
<td></td>
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<tr>
<td>HER2 mAb</td>
<td></td>
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</tr>
<tr>
<td>Trastuzumab</td>
<td>erbB2/HER2</td>
<td>Decline in LVEF, congestive heart failure</td>
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<tr>
<td>Newer HER2 inhibitors</td>
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<tr>
<td>Pertuzumab</td>
<td>erbB2/HER2</td>
<td>Decline in LVEF, congestive heart failure</td>
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<tr>
<td>Trastuzumab emtansine (TDM1)</td>
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<tr>
<td>Lapatinib</td>
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<td>Neratinib</td>
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*Continued*
### TABLE 1. Cancer Therapies and Their Associated Cardiovascular Toxicities (Cont’d)

<table>
<thead>
<tr>
<th>Class and Representative</th>
<th>Cellular Target</th>
<th>Common Cardiovascular Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>VSP (VEGF signaling pathway) inhibitors</td>
<td>VEGF-A</td>
<td>Hypertension</td>
</tr>
<tr>
<td>VEGF-A mAb</td>
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<td></td>
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<tr>
<td>Bevacizumab</td>
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<td>VEGF trap</td>
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<tr>
<td>Aflibercept</td>
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<tr>
<td>VEGFR2 mAb</td>
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<tr>
<td>Ramucirumab</td>
<td></td>
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<tr>
<td>TKI with anti-VEGF activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunitinib, sorafenib, pazopanib, axitinib, vandetanib, regorafenib, cabozantinib, lenvatinib</td>
<td>VEGF receptors (mainly VEGFR2); also other kinases: PDGFR, other kinase targets depending on the drug</td>
<td></td>
</tr>
<tr>
<td>Multitargeted TKIs</td>
<td></td>
<td></td>
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<tr>
<td>Dasatinib</td>
<td>ABL, ABL mutants (except T315I), also other kinases: SRC, KIT, PDGFR, EGFR, BRAF, DDR1, DDR2, ephrin receptors</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vascular events</td>
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<tr>
<td></td>
<td></td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>ABL, ABL mutants (except T315I), also other kinases: ARG, KIT, DDR1, NQO2</td>
<td>Vascular events (including coronary, cerebral, peripheral)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>Ponatinib</td>
<td>ABL, ABL mutants (including T315I), also multiple other kinases, including FGFR, VEGFR, PDGFR, ephrin receptor, SRC, KIT, RET</td>
<td>Vascular events (including coronary, cerebral, peripheral)</td>
</tr>
<tr>
<td></td>
<td>TIE2, FLT3</td>
<td></td>
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<tr>
<td>Other multitargeted tyrosine kinase inhibitors</td>
<td></td>
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<tr>
<td>ALK inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crizotinib</td>
<td>ALK</td>
<td>Bradycardia</td>
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<tr>
<td>Ceritinib</td>
<td></td>
<td>QTc prolongation</td>
</tr>
<tr>
<td>PI3K/Akt/mTOR inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Everolimus (mTORC1 inhibitor)*</td>
<td>PI3K/Akt/mTOR signaling pathway</td>
<td>Cardiometabolic toxicities, including hypercholesterolemia, hypertriglyceridemia, hyperglycemia</td>
</tr>
<tr>
<td>Temsirolimus (mTORC1 inhibitor)*</td>
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<tr>
<td>BTK inhibitors</td>
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<td></td>
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<tr>
<td>Ibrutinib</td>
<td>BTK</td>
<td>Atrial fibrillation</td>
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<tr>
<td></td>
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<td>Ventricular arrhythmias</td>
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<tr>
<td>MEK inhibitors</td>
<td></td>
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<tr>
<td>Trametinib</td>
<td>MEK1/MEK2</td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Immunomodulatory drugs</td>
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<td></td>
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<tr>
<td>Thalidomide</td>
<td>Lymphoid transcription factors, IKZF1 and IZKF3</td>
<td>VTE</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td>ATE</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
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<tr>
<td>Proteasome inhibitors</td>
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</tr>
</tbody>
</table>

Continued
TABLE 1. Cancer Therapies and Their Associated Cardiovascular Toxicities (Cont’d)

<table>
<thead>
<tr>
<th>Class and Representative</th>
<th>Cellular Target</th>
<th>Common Cardiovascular Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib, ixazomib</td>
<td>Ubiquitin-proteasome system</td>
<td>Cardiomyopathy (rare)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>VTE, ATE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arrhythmia</td>
</tr>
</tbody>
</table>

Immune checkpoint inhibitors

- Pembrolizumab
  - PD-1
  - Myocarditis, other CV toxicity?
- Nivolumab
  - CTLA-4
  - Myocarditis, other CV toxicity?
- Ipilimumab
  - PD-L1
  - Myocarditis, other CV toxicity?
- Atezolizumab
  - PD-L1
  - Myocarditis, other CV toxicity?
- Avelumab
  - PD-L1
  - Myocarditis, other CV toxicity?
- Durvalumab

*Only two drugs targeting the PI3K/AKT/mTOR signaling pathway, everolimus and temsirolimus, which are mTORC1 inhibitors, were approved by the Food and Drug Administration. Many other inhibitors targeting this signaling pathway are currently in clinical trials.

Abbreviations: N/A, not applicable; mAb, monoclonal antibody; VEGF signaling pathway; VTE, venous thromboembolic event; ATE, arterial thromboembolic event; TKI, tyrosine kinase inhibitor; PDGFR, platelet-derived growth factor receptor; FGFR, fibroblast growth factor receptor; ALK, anaplastic lymphoma kinase; mTORC, mTOR complex; BTK, bruton kinase inhibitor; MEK, mitogen-activated protein kinase; CV, cardiovascular.

Adapted from Moslehi.4

for treatment of HER2-positive breast cancer.47 However, in chronic myelogenous leukemia, the kinase ABL1 can become overactive via a chromosomal translocation (so-called “Philadelphia chromosome”). Small molecule inhibitors targeting ABL1 kinase (the first example being imatinib) have revolutionized treatment of chronic myelogenous leukemia.46 In many cases, the kinases being targeted also play vital roles in cardiovascular homeostasis.48 Therefore, targeting these kinases can lead to cardiovascular sequelae resulting in “on-target” toxicity. Small molecular inhibitors can also target multiple kinases. In some cases, “off-target” activity of the kinase inhibitor can result in toxicity. Because kinases play diverse roles in cardiovascular biology, associated complications with the kinase inhibitor can result in heterogeneous toxicities, causing cardiomyopathy, arrhythmias, and vascular and metabolic dysregulation.4

The first example of cardiovascular toxicity with targeted therapies occurred with the use of trastuzumab for breast cancer. In the first clinical trial, where trastuzumab was combined with standard chemotherapy regimen (including anthracyclines) for metastatic HER2-positive breast cancer, 27% of patients had evidence of cardiomyopathy, including both left ventricular dysfunction and clinical heart failure (with 16% having grade 3 or higher events).47 This prompted several strategies by the medical community, including tangential treatment (where anthracyclines were given before trastuzumab) and cardiac monitoring during trastuzumab therapy, both of which significantly lowered the rate of toxicity.48 However, small molecular inhibitors approved for chronic myelogenous leukemia were associated with a number of different toxicities, including pulmonary hypertension (with dasatinib), hyperglycemia and atherosclerosis (with nilotinib), and hypertension and vascular events (with ponatinib).51,52

Another rapidly expanding class of kinase inhibitors that can lead to cardiovascular toxicities includes therapies that target VEGF, drugs that include bevacizumab (a monoclonal antibody targeting circulating VEGF), or any number of small molecular inhibitors that target the VEGF receptors (examples include sunitinib or pazopanib).52 As a class, VEGF inhibitors are associated with hypertension, proteinuria, and (less frequently) cardiomyopathy and vascular events. Of these, hypertension is most common and seems to be an “on-target” toxicity that can occur in 25% to 87% of treated patients depending on the individual drugs.52 Blood pressure increases often occur early (within days of starting the kinase inhibitor) and can decrease when treatment is withheld. There have been multiple proposed mechanisms for how hypertension may occur. VEGF inhibition may lead to impairment of nitric oxide bioavailability, increased endothelin-1 expression, and loss of capillaries (”capillary rarefaction”), leading to increased resistance across remaining vessels and renovascular hypertension.53 More translational studies are needed to elucidate the specific contributions of each for individual therapy. The concomitant occurrence of proteinuria with hypertension in many VEGF inhibitor–treated patients is reminiscent of pre-eclampsia and has implications for clinical care of these patients, of whom urine studies should be done along with blood pressure monitoring.54 It is unclear which antihypertensive therapies are most effective for the treatment of VEGF inhibitor–associated hypertension; several groups have recommended the use of angiotensin-converting enzyme inhibitors and calcium channel blockers (such as amlodipine) as reasonable initial regimen.55

Given the rapid explosion of new kinase inhibitors approved for multiple cancer types, new cardiovascular and metabolic complications can be seen. Ibrutinib, a selective
kinase inhibitor targeting Bruton tyrosine kinase, has been approved for a number of B-cell malignancies but is associated with cardiac arrhythmias, including both atrial fibrillation and ventricular arrhythmias.\textsuperscript{56,57} Ribociclib is a new CDK4/6 inhibitor that is approved for hormone-positive breast cancer that can lead to QT prolongation and possible arrhythmias, thus requiring electrocardiographic monitoring on drug initiation.\textsuperscript{58} Mitogen-activated protein kinase inhibitors (such as trametinib), effective for treatment of a subset of melanomas, are associated with cardiomyopathy, requiring monitoring of cardiac function. PI3K and mTOR inhibitors can lead to metabolic dysfunction, such as hyperglycemia and hypertriglyceridemia, which also require monitoring.\textsuperscript{4,52} Table 1 provides a list of a number of kinases inhibitors and observed effects on the cardiovascular system. Given the dearth of data, the precise preventive and treatment strategies for each therapy are currently lacking.

In the case of “on-target” therapy, what is known regarding biologic activity of the specific kinase in the cardiovascular activity can help predict toxicities. Most commonly, however, cardiovascular sequelae of new therapies can introduce new biologic paradigms. For example, cardiomyopathy that can result with HER2 inhibitors has helped uncover a critical role for HER2 in cardiac homeostasis.\textsuperscript{59} Basic studies suggest that HER2 is expressed in the heart and serves an important role in cardiac adaptation to stress.\textsuperscript{60} The cardiovascular toxicities associated with VEGF inhibitors have helped uncover an important role for VEGF dysregulation in not only the cardio-oncology population but also, other patients.\textsuperscript{53} VEGF dysregulation, for example, plays an important role in cardiovascular complications that occur during pregnancy, including pre-eclampsia and peripartum cardiomyopathy.\textsuperscript{61,62} In this regard, cardio-oncology is often regarded not merely as a new clinical frontier in medicine but also, as a new platform for basic and clinical investigation.\textsuperscript{49}

Cardiovascular toxicities with novel therapies extend beyond kinase inhibitors. The treatment of multiple myeloma, for example, has been transformed by the introduction of immunomodulatory drugs (such as thalidomide or lenalidomide) and proteasome inhibitors (such as bortezomib and carfilzomib).\textsuperscript{63} Both therapies represent new paradigms in cancer therapy, because the cellular protein degradation machinery is targeted. Immunomodulatory drugs, for example, bind cereblon, a component of an E3 ubiquitin ligase, and promote ubiquitination and proteasome-mediated degradation of two key B-cell transcription factors.\textsuperscript{64,65} Immunomodulatory drugs have been associated with a number of cardiovascular toxic effects (Table 1). Initial clinical trials involving two immunomodulatory drugs, thalidomide and lenalidomide, showed a high risk of venous thromboembolic disease, especially in combination with high-dose dexamethasone. Therefore, thromboprophylaxis with aspirin or anticoagulation is recommended for most patients treated with immunomodulatory drugs, because they are also associated with an increased risk of arterial events, leading to a black box warning for increased risk of myocardial infarction and stroke.\textsuperscript{66} However, carfilzomib, an irreversible proteasome inhibitor, has been associated with increased risk for various cardiovascular complications, including both arterial and venous thromboembolic events, and hypertension.\textsuperscript{67} These complications come in the backdrop of patients with multiple myeloma who often have cardiovascular comorbidities and cardiovascular risk factors.\textsuperscript{66}

Finally, cancer immunotherapies have been transformative for the care of many patients with cancer and are rapidly being tested in new populations of patients with cancer. However, new cardiovascular sequelae are being seen with these therapies. Immune checkpoint inhibitors, for example, include both ipilimumab, an anti–CTLA-4 antibody, and antibodies targeting the anti–PD-1 or PD-L1. Examples of the latter include nivolumab and pembrolizumab. When used individually or in combination therapy, these therapies have significantly enhanced antitumor activity and survival in cancer types (such as melanoma) that previously had few treatment options. These therapies can cause a multitude of cardiovascular toxicities.\textsuperscript{68} Specifically, rare cases of fulminant myocarditis have been reported soon after initial exposure to the therapies.\textsuperscript{69,70} Clinically, immune checkpoint inhibitor–associated myocarditis is characterized by early progressive and refractory cardiac electrical instability, myocarditis characterized by robust presence of T-cell and macrophage infiltrates, and development of other autoimmune complications, such as myositis and rhabdomyolysis.\textsuperscript{69} Current data suggest that, although the incidence of myocarditis is infrequent (less than 1% with checkpoint inhibitor combination therapy), it has high fatality rates when diagnosed (about 50% mortality). In addition, the only risk factor that has been established is treatment with combination therapy (for example, ipilimumab and nivolumab).\textsuperscript{69} In the future, better identification of patients at risk for this severe drug side effect will be critical to ensure continuous and successful use of the therapies.

**Imaging Guidelines and Techniques for Monitoring and Preventing Cardiac Toxicity**

Cardiac imaging can have an important role in pretreatment risk assessment, early detection of cardiac injury, and identification of cardiac complications in patients receiving potentially cardiotoxic cancer treatment.

**Pretreatment risk assessment.** Given that cardiomyopathy is a common toxicity of many of the current and emerging cancer therapies, there is a growing focus on identifying patients at risk. Unfortunately, there are no established risk prediction models. Most clinicians use the presence of pre-existing cardiovascular disease or cardiovascular risk factors as markers of heightened risk for cardiotoxicity.\textsuperscript{2} However, these factors individually have poor discriminative value. Pretreatment left ventricular size and cardiac function also seem to identify patients at risk for treatment-related heart failure.\textsuperscript{11} It is estimated that approximately 7.0% of the population has asymptomatic cardiac dysfunction on screening.\textsuperscript{22} Therefore, many cancer treatment clinical trials have required normal pretreatment cardiac function as an inclusion criterion.

Assessment of cardiac function can be performed using multigated acquisition scans, echocardiography, or cardiac
MRI. Echocardiography is the preferred method because of the ability to provide comprehensive assessment of cardiac function beyond left ventricular ejection fraction (LVEF). The recent ASCO guidelines recommend pretreatment cardiac function assessment with an echocardiogram along with a comprehensive clinical history and physical examination in all patients before initiation of potentially cardiotoxic therapies.73 This recommendation is consistent with that of the American Society of Echocardiography and the European Society of Cardiovascular Imaging.74

There has also been emerging interest in the use of more advanced cardiac imaging techniques, such as myocardial strain, for pretreatment risk assessment. Myocardial strain is a measure that could be obtained through echocardiography or cardiac MRI, and it is a measure of heart muscle deformation. It can be considered to be a surrogate measure of myocardial contractility. Although strain can be measured in various directions, the two measures that are closer to routine clinical application are global longitudinal strain (GLS) and global circumferential strain (GCS). In the general cardiology literature, there is now a large body of evidence supporting the ability of myocardial strain to identify subclinical heart muscle abnormality that is not readily evident based on assessment of LVEF. Specifically in patients receiving anthracycline and/or trastuzumab therapy, pretreatment measure of GCS or GCS seems to differentiate patients who are more likely to develop cardiotoxicity.75-77

In one study, GLS greater than −17.5% (e.g., −16.0% or −12.5%) before anthracycline therapy was associated with a sixfold greater risk of heart failure or cardiac death in patients with hematologic malignancies.77 Another study has suggested that GLS greater than −16.0% in anthracycline-treated patients with LVEF between 50% and 59% by echocardiography was associated with a 4.7-fold higher risk of major adverse cardiac events.76 No such thresholds are currently available for GCS. Whether interventions based on baseline strain or LVEF abnormalities alter overall outcomes remains to be determined. However, in patients who are felt to be at elevated risk for cardiotoxicity based on abnormal or low-normal cardiac function, multiple cardiovascular risk factors, or prior cardiac history, cardiology assessment and risk factor optimization may be appropriate.

Detection of cardiotoxicity during treatment. Because identifying patients at risk for cardiotoxicity before cancer treatment is challenging, there is a necessity to screen for cardiotoxicity during cancer treatment. Clinical assessment itself is inadequate, because most patients develop asymptomatic cardiac dysfunction. Much of the literature on identifying asymptomatic cardiac dysfunction has focused on toxicities related to anthracyclines and trastuzumab. Echocardiography provides the unique ability to identify both systolic and diastolic dysfunction during treatment in a rapid fashion. The primary measure of cardiotoxicity used in clinical trials and practice is a threshold reduction in LVEF during treatment. Although this threshold has not been inconsistent in the literature, the most common definition is a greater than 10% reduction in LVEF to a value below the lower limit of normal for the laboratory and the imaging modality.2,74 Among cardiac imaging techniques, three-dimensional echocardiography provides a reproducible measurement of changes in LVEF and has been endorsed in societal expert consensus statements.2,73,74 However, LVEF as a sole marker of cardiotoxicity, especially with anthracyclines, seems to be insufficient. Large prospective studies have shown that, after a reduction in LVEF occurs, only approximately 20% of patients will have complete recovery of cardiac function, despite appropriate heart failure treatment.78 Therefore, there is a growing interest in more precise and earlier detection of myocardial changes with cancer treatment. Myocardial strain imaging and serum biomarkers have been the forerunners for this role.

The strength of strain imaging is in its robust reproducibility when using vendor-specific analytic algorithms.79 With sequential strain analysis, changes in myocardial GLS and GCS seem to precede threshold changes in LVEF used to define cardiotoxicity. The American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) position statement has suggested using a relative reduction in GLS by more than 15% to define subclinical cardiotoxicity (i.e., without a substantial reduction in LVEF).80 Such a change should prompt consideration of cardiology consultation. It should be noted that the clinical significance of reduction in GLS is not clear. In addition, whether cardiac interventions for isolated reduction in GLS improve long-term cardiovascular outcomes in patients receiving cancer therapy is not known. This question is, however, the subject of an ongoing randomized, controlled trial (the SUCCOUR trial, ACTRN 1261400341628). Other echocardiographic measures, such as mitral annular systolic and diastolic velocities and diastolic function, have been assessed as early markers of myocardial injury but have not shown robust association with cardiotoxicity.74

Screening of cancer survivors. A greater spectrum of cardiovascular disease is seen in survivors, such as cardiomyopathy, cerebrovascular disease, arrhythmias, and radiation-related changes, like pericardial constriction, valvular stenosis and regurgitation, and coronary artery disease. In pediatric cancer survivors, clear guidelines for the timing of cardiac screening have been established based on anthracycline dose, radiation exposure, and age at treatment81 (www.survivorshipguidelines.org). However, such guidelines do not exist for adult cancer survivors. The recent ASCO guidelines suggest follow-up imaging 6–12 months after completion of cancer therapy in patients considered to be at elevated risk for heart failure (e.g., age older than 60, doxorubicin dose greater than or equal to 250 mg/m², radiation therapy greater than or equal to 30 Gy with heart in the treatment field, and multiple cardiovascular risk factors). Similarly, the National Cancer Center Network survivorship guidelines recommend an echocardiogram in patients with at least one cardiac risk factor.82 The best method to identify subclinical cardiac dysfunction in these adult survivors is not clear. In pediatric cancer survivors, cardiac MRI has been shown to be the most robust technique to identify reduced LVEF followed by three-dimensional echocardiography. However, GLS and GCS measurements have been shown to identify a greater proportion
of patients with myocardial abnormalities. The clinical significance of these findings and whether interventions can alter the natural course of cardiac disease have not been established.

In patients receiving radiation therapy that may involve the heart in the treatment field, the ASE/EACVI consensus statement recommends screening echocardiography and/or functional testing for coronary artery disease 5 to 10 years after exposure, regardless of symptoms.83 Other imaging modalities, including cardiac CT and cardiac MRI, can have complementary roles in the diagnosis of pericardial disease when echocardiography is nondiagnostic. The use of coronary CT is an alternate method for detection of coronary artery disease (CAD) with high sensitivity; however, its routine use in assessment of cancer therapy–related CAD is not established. Despite the enthusiasm for detection, there is very little in the way of reversing radiation-induced cardiovascular changes other than application of general principles of atherosclerosis management.

Given the growing body of literature of overlapping risk factors in cardiovascular disease and cancer (previously described) as well as the cardiac toxicity of many cancer therapies, all cancer survivors should have risk reduction and lifestyle modifications addressed. Recently, an ABCDE approach has been proposed for cardiovascular health in patients with breast cancer and patients with prostate cancer84,85 (Sidebar 1).

### Serum Biomarkers for Detection and Prevention of Cardiotoxicity

**Troponin I.** Use of serum biomarkers to detect myocardial injury from cancer therapy is extremely attractive given that it is minimally invasive, is relatively cheap, is easily interpretable, can be readily repeated, and has low measurement variability. Specifically in patients receiving anthracyclines with or without trastuzumab, multiple serum biomarkers have been examined. Among these, marker-only elevations in Troponin I during anthracycline therapy have been consistently associated with subsequent cardiotoxicity.86,87 In the older studies of patients receiving high-dose anthracycline therapy, elevation in troponin with multiple repeated measurements around the time of treatment was associated with subsequent cardiotoxicity.87 However, single measurements also seem to have prognostic value.86 Troponin I elevations have also been reported in patients receiving sequential therapy with anthracyclines and trastuzumab. Elevation in any one troponin measure when measured before and after every trastuzumab cycle was associated with subsequent trastuzumab-associated cardiotoxicity, lower propensity to recover with heart failure therapy, and adverse cardiac outcomes in follow-up.88 Perhaps the most attractive use of troponins is to guide heart failure therapy. Although there are impressive data from a single study showing complete eradication of cardiotoxicity in patients who were treated with angiotensin-converting enzyme inhibitor with early elevation in troponin I during high-dose chemotherapy, this has not translated into routine practice.89 Other studies have shown elevated troponin I in patients receiving small molecule tyrosine kinase inhibitors and anti-VEGF therapy, but the overall data are limited.90,91 Additional research and data in this area are needed before adaptation of this testing in all patients is recommended.

**Other serum biomarkers.** Other biomarkers that have been examined to identify early cardiac injury include B-type natriuretic peptides (BNP), high-sensitivity C-reactive protein, and myeloperoxidase to name a few. Similar to troponin elevation, early elevation in myeloperoxidase in patients receiving sequential anthracycline and trastuzumab therapy was found to be predictive of cardiotoxicity.86 However, this biomarker has not been examined in other studies. BNP and NT-pro-BNP are other interesting biomarkers. Although elevations have been reported during anthracycline therapy, the predictive value for cardiotoxicity or subsequent adverse cardiac outcomes has been inconsistent.

Serum biomarkers may have a role in other emerging therapies; however, studies with these other therapies are lacking. Case reports of cardiotoxicity, for example, with immune checkpoint inhibitors have not shown consistent association with elevation troponin, even at the diagnosis of myocarditis.

Despite the enthusiasm and interest in the use of biomarkers for early detection and interventions to prevent heart

<table>
<thead>
<tr>
<th>SIDEBAR 1. ABCDE Steps for Cardiovascular Health in Cancer Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
</tr>
<tr>
<td>- Awareness of increased risk and symptoms of cardiovascular disease</td>
</tr>
<tr>
<td>- Assessment of cardiovascular risk (using established cardiovascular risk calculators)</td>
</tr>
<tr>
<td>- Aspirin: in select individuals</td>
</tr>
<tr>
<td><strong>B</strong></td>
</tr>
<tr>
<td>- Blood pressure: goal of blood pressure less than 140/90 in most patients with cancer</td>
</tr>
<tr>
<td><strong>C</strong></td>
</tr>
<tr>
<td>- Cholesterol: cholesterol measurement and treatment (if indicated)</td>
</tr>
<tr>
<td>- Cigarettes: smoking cessation in all patients</td>
</tr>
<tr>
<td><strong>D</strong></td>
</tr>
<tr>
<td>- Diet and weight management</td>
</tr>
<tr>
<td>- Diabetes: fasting glucose measurement and treatment (if indicated)</td>
</tr>
<tr>
<td>- Dose of chemotherapy and radiation; patients and physicians should be aware of the total dose of certain chemotherapies (for example, anthracyclines) and radiation</td>
</tr>
<tr>
<td><strong>E</strong></td>
</tr>
<tr>
<td>- Exercise</td>
</tr>
<tr>
<td>- Echocardiogram: per 2015 National Comprehensive Cancer Network guidelines, consider echocardiogram in select patients within 1 year of completion of anthracycline therapy</td>
</tr>
</tbody>
</table>
failure, their use is limited by the inconsistent data on the types of assay to use, the timing of measurement, and the thresholds to define toxicity or initiate cardiac interventions. However, the ASE/EACVI and the ASCO guidelines\textsuperscript{2,73,74} do include troponin measurements as a method to follow for patients during cancer therapy; however, additional guidance on how this should be measured on acted on is not provided.

**Cardiac imaging and biomarkers in the era of precision medicine.** Advanced cardiac imaging techniques and serum biomarkers are attractive methods to identify patients at risk for cardiotoxicity, which is defined as reduction in LVEF or development of heart failure. Much of the enthusiasm in the field has focused on identification of early injury, with little work on the use of these markers to offer interventions that alter meaningful outcomes for patients with cancer. However, some such studies are currently ongoing. Ultimately, to move toward a precision medicine approach, clinical and genomics information along with imaging and serum biomarker data must be combined in a clinical risk prediction model that would provide the flexibility to incorporate temporal changes in these measurements. This must be followed by studies that show that targeted interventions can prevent the development of cardiovascular toxicity without altering cancer outcomes. Such work is eagerly awaited.

**CONCLUSION**

With rapidly growing understanding of the cardiac toxicities of cancer therapies, it is important to have a growing collaboration between cardiology and oncology. There seem to be related underlying mechanisms between these two diseases. Given the plethora of cardiac toxicities from new emerging targeted therapies, a general awareness of the cardiac risks of these medications is necessary. Finally, additional work continues to be needed on the incorporation of both imaging and blood biomarkers into oncology clinical trials to determine who would benefit from these biomarkers and what interventions should be performed in this setting.

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**References**


Role of Germline Genetics in Identifying Survivors at Risk for Adverse Effects of Cancer Treatment

Lindsay M. Morton, PhD, Sarah L. Kerns, PhD, MPH, and M. Eileen Dolan, PhD

OVERVIEW

The growing population of cancer survivors often faces adverse effects of treatment, which have a substantial impact on morbidity and mortality. Although certain adverse effects are thought to have a significant heritable component, much work remains to be done to understand the role of germline genetic factors in the development of treatment-related toxicities. In this article, we review current understanding of genetic susceptibility to a range of adverse outcomes among cancer survivors (e.g., fibrosis, urinary and rectal toxicities, ototoxicity, chemotherapy-induced peripheral neuropathy, subsequent malignancies). Most previous research has been narrowly focused, investigating variation in candidate genes and pathways such as drug metabolism, DNA damage and repair, and inflammation. Few of the findings from these earlier candidate gene studies have been replicated in independent populations. Advances in understanding of the genome, improvements in technology, and reduction in laboratory costs have led to recent genome-wide studies, which agnostically interrogate common and/or rare variants across the entire genome. Larger cohorts of patients with homogeneous treatment exposures and systematic ascertainment of well-defined outcomes as well as replication in independent study populations are essential aspects of the study design and are increasingly leading to the discovery of variants associated with each of the adverse outcomes considered in this review. In the long-term, validated germline genetic associations hold tremendous promise for more precisely identifying patients at highest risk for developing adverse treatment effects, with implications for frontline therapy decision-making, personalization of long-term follow-up guidelines, and potential identification of targets for prevention or treatment of the toxicity.

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germline genomics research in relation to nonmalignant and malignant adverse effects of therapy. We then provide a roadmap for future research that is needed to realize the promise of employing germline genetics to bring precision medicine into survivorship.

**PERSPECTIVES ON GENOMICS RESEARCH AND HUMAN HEALTH**

Inherited predisposition to cancer has been recognized for well over a century based on the identification of families with strikingly elevated risk for breast cancer. Over the last several decades, specific genes that underlie many rare inherited disease predisposition syndromes have been systematically identified. More recently, studies increasingly have attempted to identify common genetic variants that could be associated with cancer risk in the general population as well as variants that could be associated with response to cancer treatment. Those studies generally have followed the path described above, albeit at a slower pace, with fewer studies completed thus far. As with other complex diseases, much of the initial research has focused on candidate genes, the results of which typically either have not been investigated or have failed to replicate in independent populations. Only more recently has the field begun to include agnostic, genome-wide study designs (Table 1). The good news is that pharmacogenomic and radiogenic studies tend to have larger effect sizes than complex disease susceptibility studies primarily because the relevant environmental factors (drug and radiation exposure, respectively) are known. The challenge, however, is implementing large, well-powered studies with homogenous treatment exposures and consistent measures of adverse effects, with replication of results in independent populations.

**PRACTICAL APPLICATIONS**

- Certain adverse effects of cancer therapy are thought to have a significant heritable component.
- Most previous research on germline genetic susceptibility to adverse effects has narrowly focused on variation in candidate genes and pathways, and few of the findings have been replicated in independent populations.
- Advances in understanding of the genome, improvements in technology, and reduction in laboratory costs have led to recent genome-wide studies, which agnostically interrogate common and/or rare variants across the entire genome, enabling identification of novel genes and pathways that may impact the development of adverse effects.
- Large-scale collaborative efforts are essential for replicating results from genomics studies of adverse treatment effects to translate the findings into clinical practice.
- In the long-term, validated germline genetic associations hold tremendous promise for more precisely identifying patients at highest risk for developing adverse treatment effects, with implications for frontline therapy decision-making, personalization of long-term follow-up guidelines, and potential identification of targets for prevention or treatment of the toxicity.

**NONMALIGNANT ADVERSE EFFECTS OF CANCER TREATMENT**

Radiotherapy

Toxicities following radiotherapy vary depending on the tumor site and surrounding normal tissues exposed. For example, common toxicities following radiotherapy for head and neck tumors include oral mucositis, dysphasia, and xerostomia resulting from damage to the oral epithelium and salivary glands, development of fibrosis in the pharynx, as well as inflammation. Pelvic radiotherapy used for treatment of prostate, cervical, bladder, and rectal cancers can cause intestinal, bowel, and bladder damage that can result in adverse gastrointestinal and urinary effects including bleeding, pain, frequency, and urgency. Local radiation damage can also lead to subsequent systemic effects. For example, damage to the oral cavity can lead to poor dental hygiene, increased susceptibility to oral infections, oral pain, and difficulty chewing and swallowing that can in turn result in sleep disturbances, nutritional deficiencies, and overall decrease in quality of life. Similarly, damage to the gastrointestinal tract can lead to chronic dysfunction resulting in altered intestinal transit and nutritional malabsorption.
It has long been recognized that substantial variation exists among patients in the incidence and severity of normal tissue reactions to radiotherapy. Individual variation of normal tissue response for a given radiation dose was first described in the scientific literature in 1936, with the publication of a sigmoid dose response curve for the development of skin telangiectasia. The hypothesis that radiation sensitivity may be heritable is supported by the existence of rare genetic syndromes associated with hypersensitivity to radiation, where rare mutations in genes involved in DNA double-strand break repair, such as \textit{ATM} (ataxia telangiectasia mutated), \textit{NBS1} (Nijmegen breakage syndrome), \textit{MRE11} (ataxia telangiectasia-like disorder), and \textit{LIG4} (DNA ligase IV deficiency), result in syndromes characterized by extreme radiosensitivity and increased risk for developing cancer. The variable responses to radiotherapy observed in patients who are treated with protocols involving similar dosimetric characteristics but are not affected by one of these rare syndromes suggest the importance of common genetic factors.

The biologic mechanisms underlying development of radiotherapy adverse effects involve general processes common to multiple normal tissues, such as fibrosis, necrosis, inflammation, and vascular damage. However, the relative importance of specific genes and pathways may vary depending on the specific normal tissues involved and the endpoints of interest. For example, pathways involved in repair of muscle damage may be more important in the

**FIGURE 1.** Examples of Radiotherapy and Systemic Therapy–Related Adverse Effects on a Range of Organ Systems

Both nonmalignant (blue font) and malignant (red font) adverse sequelae can result from systemic therapy, radiation, or the combination. Studies increasingly are identifying germline genetic variants that affect individual patients’ susceptibility to developing adverse effects after specific cancer therapies.
context of bladder function following pelvic radiotherapy, whereas pathways regulating the development of collagen deposition and fibrosis may be more important in development of lung damage. There are also differences in the biologic pathways underlying early versus late effects of radiation for most adverse effects. Thus, studies aiming to identify genetic risk factors must take tissue specificity and endpoint specificity into consideration at the design stage.

Early studies of SNP-toxicity associations focused on candidate genes known to be important in cellular radiation response from in vitro radiobiologic studies. These include genes involved in DNA damage response, cellular survival, free radical metabolism, wound healing, and inflammation. While those early studies were limited by high genotyping costs, incomplete understanding of the genetic architecture of the human genome, and lack of attention to the confounding effects of ancestry, some associations were successfully replicated. For example, the missense SNP rs1139793 in TXNRD2 was significantly associated with radiation-induced fibrosis after breast cancer in a study of candidate genes involved in reactive oxygen species metabolism.53 Furthermore, rs1139793 was significantly associated with TXNRD2 mRNA expression in blood, suggesting a functional impact of the SNP. In another candidate gene study, rs1800629 in the inflammatory cytokine TNF showed a replicated association with skin toxicity in breast cancer survivors.54 A study of patients with non–small cell lung cancer found that the functional promoter variant rs2868371 in HSPB1 was significantly associated with pneumoni̇tis following chemoradiation,55 and this same variant was subsequently shown to be associated with radiotherapy-induced esophagitis, suggesting it may play a broad role in radiosensitivity across different tissue types.56 Although early studies of the common SNP rs1801516 in ATM showed inconclusive results, a recent

**TABLE 1.** List of Genome-Wide Association Studies of Selected Treatment-Related Adverse Effects

<table>
<thead>
<tr>
<th>Treatment, Study Reference</th>
<th>Adverse Effect</th>
<th>Study Population, by Ancestry</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nonmalignant Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy17</td>
<td>Erectile dysfunction</td>
<td>African American (79)</td>
</tr>
<tr>
<td>Radiotherapy18</td>
<td>Rectal incontinence</td>
<td>European (579)[516]</td>
</tr>
<tr>
<td>Radiotherapy19</td>
<td>Overall late toxicity</td>
<td>European and European American (741)[633 and 368]</td>
</tr>
<tr>
<td>Radiotherapy20</td>
<td>Increased urinary frequency</td>
<td>European and European American/Canadian (1,564; meta-analysis of four studies: 597, 527, 290, 151)</td>
</tr>
<tr>
<td>Radiotherapy20</td>
<td>Decreased urinary stream</td>
<td>European and European American/Canadian (1,564; meta-analysis of four studies: 597, 527, 290, 151)</td>
</tr>
<tr>
<td>Paclitaxel21</td>
<td>Neuropathy</td>
<td>European (144)</td>
</tr>
<tr>
<td>Paclitaxel22</td>
<td>Neuropathy</td>
<td>European American (855)[154 European American; 117 African American]</td>
</tr>
<tr>
<td>Paclitaxel/docetaxel23</td>
<td>Neuropathy</td>
<td>Diverse (1,570)[1,357 European American; 213 African American][789 European American; 90 African American; 56 other]</td>
</tr>
<tr>
<td>Docetaxel24</td>
<td>Neuropathy</td>
<td>European American (623)</td>
</tr>
<tr>
<td>Vincreistine25</td>
<td>Neuropathy</td>
<td>Diverse (321)[209 European American; 43 African American; 2 Asian; 44 Hispanic; 23 other]</td>
</tr>
<tr>
<td>Platinating (combination)26</td>
<td>Neuropathy</td>
<td>Korean (96)[247]</td>
</tr>
<tr>
<td>Bortezomib27</td>
<td>Neuropathy</td>
<td>European (469)[114]</td>
</tr>
<tr>
<td>Bortezomib28</td>
<td>Neuropathy</td>
<td>European (646)</td>
</tr>
<tr>
<td>Cisplatin29</td>
<td>Neuropathy</td>
<td>European American (680)</td>
</tr>
<tr>
<td>Cisplatin30</td>
<td>Ototoxicity</td>
<td>European American (511)</td>
</tr>
<tr>
<td>Cisplatin31</td>
<td>Ototoxicity</td>
<td>Diverse (238)[European American, African American, and other][68]</td>
</tr>
<tr>
<td><strong>Subsequent Neoplasms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy32</td>
<td>Any subsequent neoplasm</td>
<td>European American (178)[227]</td>
</tr>
<tr>
<td>Radiotherapy33</td>
<td>Breast cancer</td>
<td>European American (2378)[603]</td>
</tr>
<tr>
<td>Radiotherapy, chemotherapy34</td>
<td>MDS/AML</td>
<td>European American (230)[165]</td>
</tr>
</tbody>
</table>

*Replication refers to any study that performs a second association study in another cohort within the same publication.

**Received additional chemotherapeutic drugs; however, study was intended to evaluate taxane-induced neuropathy.

Abbreviation: MDS/AML, myelodysplastic syndrome/acute myeloid leukemia.
meta-analysis of individual patient data provides convincing evidence that the minor allele of this SNP is associated with an increased risk of overall radiotherapy-induced acute and late toxicity,\(^67\) confirming that both common and rare ATM variants contribute to general radiosensitivity. In contrast, a replicated association has been reported between rs1800469 in TGFBI and esophagitis,\(^58,\,^59\) whereas a large meta-analysis of individual patient data (2,782 patients, 11 independent studies) reported no association of this SNP with radiotherapy-induced fibrosis,\(^60\) indicating that some SNPs show tissue specificity.

GWAS have begun to identify additional, novel radiosensitivity loci within genes not previously known to be involved in cellular or tissue response to radiation. The first radiogenomics GWAS, though underpowered, was able to detect a risk locus within the FSHR gene associated with erectile dysfunction following radiotherapy for prostate cancer based on 79 cases.\(^17\) A much larger (> 1,500 patients) three-stage GWAS of overall late toxicity including urinary and rectal effects in patients with prostate cancer identified a locus in TANC1,\(^19\) which is expressed in myoblasts and plays a central role in regeneration of damaged muscle. A recent individual patient data meta-analysis of four GWAS of late toxicity in prostate cancer radiotherapy patients identified two more risk SNPs: rs17599026 in KDM3B and rs1800469 in DNAH5 associated with increased urinary frequency and rs7720298 in DNAH5 associated with decreased urinary stream.\(^20\) Notably, these SNPs lie within genes that are expressed in tissues likely underlying these symptoms, including the bladder, which is exposed to radiation during treatment of prostate cancer. Indeed, the genes identified via GWAS of radiotherapy toxicity have not previously been implicated in cellular or tissue response to radiation, but initial laboratory data suggest they may be involved in key radio-response pathways such as muscle cell regeneration after radiation induced damage (TANC1) and DNA double-strand break repair following irradiation (KDM3B; unpublished data). Ongoing functional studies are underway to further characterize these genes. Expanded efforts currently underway through the Radiogenomics Consortium\(^61\) and the REQUIITE study\(^62\) are expected to uncover additional risk SNPs and will allow for investigation of gene-environment interaction, investigation of effect modifiers, and validation of prior SNP-toxicity associations.

Systemic Therapy
Toxicities related to systemic therapy, such as peripheral neuropathy, myelosuppression, hepatotoxicity, ototoxicity, pancreatitis, cardiotoxicity, and osteonecrosis, could be lifelong and often have debilitating effects on a survivor’s physical and psychological well-being. Below, we focus on chemotherapy-induced peripheral neuropathy and ototoxicity to exemplify current understanding of the genomics of nonmalignant adverse effects of systemic therapy.

Chemotherapy-induced peripheral neuropathy. Chemotherapy-induced peripheral neuropathy is one of the most common adverse effects of chemotherapy\(^63,\,^64\) and may arise as a result of mechanistically different chemotherapeutics.\(^65\) In part because of a paucity of genetically diverse human models of chemotherapy-induced peripheral neuropathy, there are no preventive measures or effective treatments for this devastating adverse drug effect.\(^66\) Patient demographics (i.e., race and history of neuropathy) and treatment (i.e., cumulative dose and drug exposure) factors have been associated with chemotherapy-induced peripheral neuropathy.\(^67,\,^69\) Race was also a major predictor of paclitaxel induced neuropathy, with patients of African descent experiencing increased risk of grade 2 to 4 as well as grade 3 to 4 peripheral neuropathy compared with others.\(^23\) In addition, peripheral neuropathy resulting from cisplatin treatment has been shown to be negatively associated with self-reported health and physical activity level and positively correlated with weight gain after treatment, suggesting a less active lifestyle due to complications of neuropathy.\(^29\)

Early studies exploring the genetic contribution to chemotherapeutic toxicities relied heavily upon candidate gene approaches, associating SNPs in genes encoding known drug metabolizing enzymes, DNA repair pathways, receptors, and transporters. For example, SNPs in GSTP1,\(^70,\,^71\) ABCG2,\(^72\) XPC,\(^73\) and ERCC1\(^74\) were associated with cisplatin-induced neuropathy when evaluated singly, but the findings did not replicate in a subsequent GWAS.\(^29\) SNPs in candidate genes also were reported to be associated with paclitaxel,\(^74,\,^78\) and docetaxel-\(^29\) induced neuropathy.

There have been a number of GWAS of chemotherapeutic-induced peripheral neuropathy associated with vincristine,\(^25\) paclitaxel,\(^21,\,^23\) docetaxel,\(^24\) bortezomib,\(^27,\,^28\) oxaliplatin,\(^80\) and cisplatin.\(^29\) GWAS of paclitaxel-induced peripheral neuropathy in a large cooperative trial identified a signal in EPHAS (rs7349683)\(^22\) that was replicated by others,\(^21,\,^81\) but interestingly also met replication significance (p < .05) in a study of cisplatin-induced neuropathy.\(^29\) A common polymorphism in FGD4 (rs10771973), a congenital peripheral neuropathy gene, also was associated with paclitaxel-induced neuropathy and was replicated in an African American cohort.\(^23\) More recent work has identified a panel of SNPs associated with increased risk of grade 3 to 4 paclitaxel-induced peripheral neuropathy in patients of European descent,\(^23\) but they were not in agreement with a previous GWAS of paclitaxel-induced neuropathy.\(^23\) However, both studies implicated the importance of the Wnt pathway (Wntless [WLS]\(^72\) and frizzled [FZD3]\(^73\)) in paclitaxel-induced peripheral neuropathy. The most compelling study focused on vincristine-induced peripheral neuropathy in a pediatric population, identifying a genome-wide significant SNP in CEP72, with accompanying functional studies showing that knockdown of the gene resulted in greater sensitivity to vincristine\(^25\) and subsequent replication in adult patients with acute lymphoblastic leukemia.\(^82\)

A recent large-scale GWAS of testicular cancer survivors estimated that cisplatin-induced peripheral neuropathy was significantly heritable (h^2 = 0.74; p = .03).\(^29\) A transcription-wide association study implicated lower (genetically determined) expression of RPRD1B in cisplatin-induced peripheral neuropathy, which was replicated in an independent cohort.
of patients who developed drug-induced polyneuropathy.98 Importantly, RPRD1B functions in DNA repair, transcription, and cell cycle control and may be a target for drug development.83

**Ototoxicity.** Ototoxicity (including both hearing loss and tinnitus) is another notable side effect of systemic therapy that can create functional limitations, ranging from impairment of speech development and academic achievement in children to detrimental effects on quality of life, socialization, and cognition in adults.84 In contrast to chemotherapy-induced peripheral neuropathy, ototoxicity results primarily from the use of platinating agents, specifically cisplatin.85,86 Cisplatin is used in the treatment of many adult-onset (cervical, endometrial, head/neck, lung, ovarian, and testicular) and pediatric (germ cell tumors, medulloblastoma, neuroblastoma, osteosarcoma, and retinoblastoma) malignancies, making it one of the most commonly applied chemotherapeutic agents worldwide. The incidence of hearing loss following cisplatin treatment is high and dependent on the cumulative dose and regimen. For example, in testicular cancer survivors receiving cisplatin, 80% had some degree of hearing loss and 18% had severe to profound hearing loss as measured by audiometry.4

Until recently, genetic studies of cisplatin-associated ototoxicity have been almost exclusively conducted in small pediatric cohorts (130–254 patients) that predominantly involved candidate gene investigations87–90 with conflicting results.91,92 In adults, previous candidate gene studies were confounded by agents known to induce ototoxicity, including vincristine93–95 and cranial radiotherapy.96–99

The first GWAS of cisplatin-induced ototoxicity identified an association with a genetic variant (rs187232) in ACYP2 in pediatric patients with brain tumors, with replication of results in a second cohort of pediatric patients31 as well as three additional studies.100–102 Another GWAS of cisplatin-induced ototoxicity was performed in testicular cancer survivors and identified a significant SNP (rs62283056) in the first intron of Mendelian deafness gene WFS1 ( wolframin ER transmembrane glycoprotein) associated with cisplatin-induced hearing loss10 that was replicated in an independent population of patients with testicular cancer when evaluating the same phenotype (geometric mean).102 That SNP is an expression quantitative trait locus (eQTL) for the WFS1 gene, with the risk (and minor) allele being associated with lower expression of the gene. Deleterious mutations in WFS1 cause Wolfram syndrome, a Mendelian disorder characterized by deafness and other neurodevelopmental conditions. The shared genetic architecture between cisplatin-induced ototoxicity with Mendelian forms of deafness could potentially impact those who live with disabling deafness. Notably, both variants identified through GWAS are extremely rare in the East Asian population (0.011 for rs1872328 in ACYP2 and 0.003 for rs62283056 in WFS1) pointing to the importance of inclusion of diverse cohorts in future pharmacogenomics studies to ensure that the benefits of genomic medicine are realized for all.103

**MALIGNANT ADVERSE EFFECTS OF RADIOThERAPY AND SYSTEMIC THERAPY**

**Radiotherapy**

The development of a subsequent malignancy substantially impacts morbidity and mortality and is thus one of the most serious treatment-related adverse effects. Detailed studies of cancer survivors and other populations exposed to ionizing radiation demonstrate increased risk for a wide range of malignancy types.104–108 The highest risks (> fivefold) have been reported for malignancies of the skin (basal cell carcinoma), soft tissue, central nervous system, bone, thyroid, and breast, whereas more modest but still significantly elevated risks have been reported for malignancies of the lung, gastrointestinal tract, pancreas, bladder, and salivary gland. Risks generally increase linearly with increasing radiation dose, with the exception of thyroid cancer, for which a downturn in risk is evident above doses of approximately 20 Gy. Most radiation-associated subsequent malignancies do not appear for at least 5 to 10 years following exposure, and the elevated risks persist for decades. Several factors have been identified to modify radiotherapy-related risks for subsequent malignancies, including certain systemic therapies as well as age at exposure, with generally higher risks for younger ages at exposure.

Candidate gene studies of radiotherapy-related subsequent malignancies generally have focused on genetic variants in DNA damage detection and repair mechanisms, as reviewed in 2015.109 For example, the Women’s Environmental Cancer and Radiation Epidemiology (WECARE) Study is a multicenter U.S.-based case-control study of contralateral breast cancer among breast cancer survivors.110 In that study, sequencing of ATM for 708 cases and 1,397 controls revealed a stronger radiation dose-response relation among women who carried deleterious missense variants (excess relative risk / Gy = 2.6; 95% CI, 0.0–10.6) than among those without deleterious (i.e., “tolerated”) missense ATM variants (ERR/Gy = 0.8; 95% CI, 0.1–3.6) or without any missense ATM variants (ERR/Gy = 0.0; 95% CI, < 0–0.3).111 Intriguingly, the findings were more pronounced among women diagnosed with breast cancer at a younger age or whose contralateral breast cancer occurred 5 years or more after first primary breast cancer. In contrast to those results, a similar pattern was not found for women who carry deleterious BRCA1/2 mutations.112 In an expanded study (1,459 contralateral breast cancer cases, 2,126 unilateral breast cancer controls), common genetic variants known to be associated with breast cancer also were associated with risk of contralateral breast cancer, but the risk patterns did not differ significantly by prior treatment exposures.113 A candidate gene study of central nervous system tumors also has been conducted among childhood cancer survivors, including 82 cases and 228 matched controls in the initial study set and an additional 25 cases and 54 controls in a replication set.114 That study found marginal associations with a number of SNPs known to be associated with central nervous system tumors in adults, but, similar to the WECARE study, did not clearly demonstrate differences by prior treatment exposures.
Overall, the candidate gene studies generally have not had sufficient sample size to conduct analyses stratified by homogenous treatment exposures with specific phenotypes and/or have not replicated results in independent populations.

More recently, several GWAS of subsequent malignancies after radiotherapy have been conducted. A two-stage GWAS investigated risk of any subsequent malignancy after childhood Hodgkin lymphoma, using a discovery set of 96 cases (61% breast cancer) and 82 controls (followed for ≥27 years with no subsequent malignancy reported) from the Childhood Cancer Survivor Study and a replication set of 119 cases (89% breast cancer) and 108 controls from high-risk cancer predisposition clinics. That study found a significant association with several variants at chromosome 6q21 that were correlated with expression of PRDM1, a zinc finger transcriptional repressor, and radiation-induced MYC repression. Notably, in the replication set, the association was restricted to younger cases and controls.

Another GWAS investigated risk of breast cancer among survivors of any childhood malignancy, leveraging data from two large-scale cohort studies of childhood cancer survivors that both have available DNA, detailed treatment data, and long-term, systematic follow-up: the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort. Comparing 207 female survivors of European descent who developed breast cancer with 2,774 survivors who had not developed any subsequent malignancy as of the date of last follow-up, the GWAS identified a relatively common locus on 1q41 as well as a rare variant at 11q23 that both appeared to be associated with breast cancer risk, but only among survivors who had received at least 10 Gy radiation exposure to the breast (1q41: rs4342822, nearest gene PROX1, risk allele frequency in controls = 0.46; HR 1.92; 95% CI, 1.49–2.44; p = 7.09 × 10^{-9}; 11q23: rs74949440, TAGLN, risk allele frequency in controls = 0.02; HR 2.59; 95% CI, 1.62–4.16; p = 5.84 × 10^{-9}). Because genotyping was conducted in the full cohorts for both the Childhood Cancer Survivor Study and the St. Jude Lifetime Cohort, additional analyses of other specific subsequent malignancies are expected to be published in coming years.

Systemic Therapy
Certain cytotoxic agents, particularly alkylating agents, platinum-based compounds, and topoisomerase II inhibitors, are well-established very strong risk factors for chemotherapy-related myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). Numerous studies have investigated the genomics of chemotherapy-related MDS/AML, but most have been candidate gene studies related to drug metabolism, DNA damage detection, and DNA repair, as reviewed recently. Unfortunately, as with other candidate gene studies, few of these results have been investigated or replicated in independent populations.

A single GWAS of chemotherapy-related MDS/AML used a two-stage design (discovery: 80 cases, 150 cancer-free controls; replication: 70 cases, 95 controls). Three SNPs were identified as top associations, including rs1394384, which is intronic to ACC11, encoding an amiloride-sensitive sodium channel; rs1199098, which is in linkage disequilibrium with IPMK, in the inositol phosphokinase family; and rs1381392, which is not near any known genes. Intriguingly, the results were stronger when the cases were restricted to those with chromosome 5 and/or 7 abnormalities, which are typically associated with prior exposure to alkylating agents, but detailed chemotherapy exposure data were not available.

Systemic therapy is also increasingly understood to play a role in risk for solid tumors. Elevated risks have been reported for certain alkylating agent–containing regimens with lung cancer and gastrointestinal tract malignancies, for example, whereas gonadotoxic chemotherapy has been associated with decreased risk of developing subsequent breast cancer. In the WE CARE study, SNPs in genes associated with metabolism of breast cancer chemotherapeutic agents did not appear to alter the protective effect of chemotherapy on contralateral breast cancer risk. Beyond this study, the genomics of chemotherapy-related risks of solid tumors has not been investigated.

**FUTURE DIRECTIONS**
A major goal in cancer survivorship research is to improve the understanding of factors that contribute to treatment-related toxicities. The establishment of long-term cancer survivorship studies in children and young adults is especially important because patients are often cured and thus remain at lifelong risk for the emergence of either the late effects of cancer therapy or the long-term persistence of acute-onset toxicity. The focus of precision cancer medicine in recent years has been on identifying somatic alterations in individual patient tumors and attempting to match those mutations with specific therapeutic strategies. To bring precision medicine into survivorship, a better understanding of the impact of germline genetic variation on incidence of treatment-related adverse effects is critical. However, much work remains to realize the promise of precision medicine in cancer survivorship. Above, we reviewed the current state of knowledge surrounding the genomics of both nonmalignant and malignant treatment-related adverse effects. In general, advances in our understanding have been hampered by a number of key methodologic limitations that must be addressed in future studies, and large-scale collaborative efforts are essential.

The difficulty and expense associated with large, prospective pharmacogenomics and radiogenomics studies is the primary challenge facing studies of the genomics of treatment-related adverse effects, which require the collection of DNA, detailed treatment data, and long-term systematic follow-up for well-defined outcomes in large numbers of patients. Increasingly, investigators are therefore leveraging clinic-based cohorts and clinical trials to conduct such studies. For example, the International Radiogenomics...
Consortium formed with the goal of fostering collaborative efforts to pool data from existing cohorts and clinical trials to increase sample sizes for genetic studies of radiotherapy adverse effects. Although these populations may not be wholly representative of all cancer survivors in the general population, they have tremendous potential for advancing the field. In studies of late adverse effects, particularly subsequent malignancies, the need for very long-term follow-up is an added challenge particularly in prospectively designed studies. A number of ongoing cohort studies of cancer survivors, such as the Childhood Cancer Survivor Study, have both detailed treatment data and systematic long-term follow-up. Recently collected DNA make these studies an invaluable contribution to the genomics of survivorship, although biases in sample collection due to either nonresponse or survival bias must be considered in the design of studies and interpretation of results.

A further challenge in the field derives from potential heterogeneity in treatment effects and phenotypes. Studies of the genomics of survivorship would optimally be designed with very well-defined outcomes ascertained in patient populations that are homogeneous with respect to treatment exposures and other key factors that may modify risk for adverse effects, such as age at exposure. An example of this is the Platinum Study, an international consortium of cancer centers that studies cisplatin-treated testicular cancer survivors. The study includes detailed collection of dose information for all drugs, systematic evaluation of human hearing using state of the art audiometric methods, and collection of extensive health information related to other toxicities. The REQUITE study aims to achieve a similar goal in radiogenomics, by using standardized data collection and patient reported outcome forms to prospectively assess late radiation toxicity in patients with breast, lung, and prostate cancer. With the exception of some cancers, the last several decades have seen dramatic changes in treatment approaches, including changes in doses or intensity of therapy, development of novel radiotherapy techniques, and introduction of new systemic therapies, but the impacts of these changes on risk for adverse effects is often poorly understood, and the joint effects with genetic variants are unknown. For example, advances in radiation delivery technology and treatment planning have allowed clinicians to optimize radiotherapy, but newer delivery methods can result in more variable dose distribution in surrounding normal tissues, with larger volumes receiving low doses. The effect of genetic factors on toxicity risk may differ depending on the radiation dose and volume of tissue exposed. Radiation and systemic cancer therapies can interact and synergistically impact adverse effects, and this interplay is becoming increasingly complex with the introduction of targeted biologics and immunotherapies. The studies described above for chemotherapy-induced peripheral neuropathy and ototoxicity emphasize the importance of conducting studies in patients with homogeneous treatment exposures, since different variants have been identified for the same chemotherapeutic-induced toxicity. Additionally, differences in the variants identified for specific phenotypes (e.g., specific types of subsequent malignancies) highlights the importance of studying well-defined outcomes.

The lack of available data and potential heterogeneity in treatment effect impact the likelihood of discovering genetic factors that influence treatment-related adverse effects. An important determinant of statistical power is the estimated effect size. Currently, complex human traits and diseases are generally thought to be polygenic, with heritable components arising from a combination of rare variants with relatively strong effects and many common variants, each of which has a weak effect. The extent to which this paradigm is applicable to the genomics of treatment-related adverse effects is as yet unknown but has important implications for statistical power because it is difficult to imagine large-scale survivorship studies of more than 10,000 patients with a specific adverse effect. However, to date, some of the GWAS of treatment-related adverse effects have identified common variants with relatively high risk estimates (> twofold risk per allele, compared with 1.1- to 1.2-fold for most adult sporadic diseases) consistent with studies demonstrating pharmacogenomic studies tend to have larger effect sizes, as described above.

Once genetic variants associated with specific adverse events have been identified, risk prediction models constructed in independent patient populations are needed, combining genetic information with current models based primarily on treatment exposures. Evidence is beginning to emerge from modeling and experimental approaches that supports the hypothesis that incorporation of genetic or other biologic data into toxicity risk prediction models can result in improvements in sensitivity and specificity. For example, a data simulation study showed that incorporation of SNPs can improve the area under the receiver operating characteristic curve of a radiation dose-based model, and the same concept would apply to a model of systemic therapy. As expected, the magnitude of improvement increased with increasing number of SNPs and was affected by assumptions about minor allele frequency, effect size, and toxicity prevalence. If the majority of risk SNPs has very modest effect sizes (< 1.2), hundreds of SNPs are needed to substantially improve models; in contrast, if some risk SNPs have larger risk estimates (1.2–2.0), fewer than 100 may be sufficient to improve models to an extent that is clinically meaningful. With large-scale collaboration for variant discovery, validation, and translation into risk prediction models, a substantial number of patients have the potential to benefit from precision medicine not only in selecting the optimal therapeutic strategy to shrink or eradicate their tumor, but also to estimate their acute and long-term treatment-related risks.
References


“How Much Time Do I Have?”: Communicating Prognosis in the Era of Exceptional Responders

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OVERVIEW

Prognostication is the science by which clinicians estimate a patient’s expected outcome. A robust literature shows that many patients with advanced cancer have inaccurate perceptions of their prognosis, thus raising questions about whether patients are truly making informed decisions. Clinicians’ ability to communicate prognostic information is further complicated today by the availability of novel, efficacious immunotherapies and genome-guided treatments. Currently, clinicians lack tools to predict which patients with advanced disease will achieve an exceptional response to these new therapies. This increased prognostic uncertainty on the part of clinicians further complicates prognostic communication with patients. Evidence also suggests that many oncologists avoid or rarely engage in prognosis-related communication and/or lack skills in this area. Although communication skills training interventions can have a positive impact on complex communication skills for some clinicians, there is no one-size-fits-all approach to improving patient-clinician communication about prognosis. Yet improving patient understanding of prognosis is critical, because patient understanding of prognosis is linked with end-of-life care outcomes. Solutions to this problem will likely require a combination of interventions beyond communication skills training programs, including enhanced use of other cancer clinicians, such as oncology nurses and social workers, increased use of palliative care specialists, and organizational support to facilitate advance care planning.

Prognostication is the science by which clinicians estimate the expected outcome for a particular patient, in a particular clinical scenario. In some cases, prognostication refers to clinicians’ estimation of the overall possibility of cure, wherein the prognostic estimate is binary (as in, “yes, cure is possible,” or “no, it is not”). In other cases, prognostication involves the clinician estimating the likelihood of cancer recurrence after receiving potentially curative therapy, such as surgery, or the chance of survival 5 years after cancer diagnoses. Whichever way the clinician formulates prognosis, by rendering one, the clinician aims to convey critically important information to patients and their family about what the future holds. Although the bioethical principle of autonomy suggests that knowing one’s prognosis is essential (as in, “I have a right to know”), prognostication is also instrumental in the decision-making process about cancer treatments. Indeed, prognostic information must be shared and understood as one essential part of the process of “shared decision-making,” a topic of growing importance in modern cancer care.

WHY IS PROGNOSTICATION IMPORTANT?

Shared decision-making is defined as the process by which “clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences.” For more than a decade, the National Academy of Medicine has recommended shared decision-making as the gold-standard process by which medical decision-making should occur; others uphold shared decision-making as the pinnacle of person-centered care. Essential components of shared decision-making include: (1) discussion of the choice at hand, (2) a detailed review of potential risks, benefits, and tradeoffs for each treatment option, and (3) the solicitation and discussion of individual values, goals, and preferences important to that particular patient.

Regardless of the decisional framework used, understanding one’s prognosis is fundamental to making an informed treatment decision. Imagine, for example, a patient with acute myeloid leukemia who is facing a choice about whether to pursue high-dose induction chemotherapy, low-dose chemotherapy, or supportive care alone. The possibility of achieving a complete remission might be as high as 50% to 85% with high-dose chemotherapy, and this treatment might also confer a long-term chance of cure, yet this treatment also inherently involves some risk of early death. On the other hand, remission and cure are far less likely with...
low-dose chemotherapy, and they are not possible with supportive care alone. Although low-dose treatment poses very little to no risk of early death from toxicity, this reduction in risk comes at great cost if one prioritizes a chance at cure or highly values prolonged survival.

How a patient approaches these important tradeoffs is influenced by their understanding about the possible (and most likely) outcomes. For example, if a patient does not understand that their disease is potentially curable, that patient may make fundamentally different decisions about the tradeoffs inherent in receiving chemotherapy, particularly regarding side effects and risks. On the other hand, a patient who understands that their disease is incurable may prioritize these factors differently, perhaps favoring less-aggressive interventions in an effort to prioritize overall quality of life and symptom control, with less emphasis on prolonging life. A growing evidence base supports the connection between patient understanding of prognosis and treatment preferences, as we discuss further below.

**HOW WELL DO PATIENTS WITH CANCER UNDERSTAND THEIR ILLNESS?**

Several studies suggest that patients with advanced solid tumors and hematologic cancers alike harbor inaccurate perceptions of their prognosis. In a study of nearly 1,200 patients who received chemotherapy for metastatic lung or colorectal cancer, investigators used surveys to assess patients’ understanding of the intent of their chemotherapy. In this study, 69% of those with lung cancer and 81% of those with colorectal cancer did not understand that their chemotherapy was unlikely to yield a cure, and that it was largely being prescribed with palliative intent. Similarly, an international study showed that 55% of 1,390 patients with cancer who were receiving palliative care inaccurately reported their cancer as being curable. In a study of 50 patients with advanced gastrointestinal cancers, investigators assessed patients’ information preferences, understanding of prognosis and treatment goals, and overall quality of life and mood. Although most patients (75%) wanted to know as much as possible about their cancer, 50% thought the goal of their palliative treatment was to “cure the cancer.”

In a study of 43 patients age 60 or older with acute myeloid leukemia or high-risk myelodysplastic syndrome, investigators assessed prognostic understanding and treatment preferences about intensive or nonintensive approaches. Ultimately, 74% of patients estimated their chance of cure at 50% or greater, whereas 89% of the time their physicians estimated it at 10% or less. Most patients (63%) also reported not being offered other treatment options, despite evidence of such conversations being universally documented in the clinical record. Similarly, in a prospective national cohort study of patients undergoing stem cell transplantation, investigators found that although patients and physicians were both relatively accurate at predicting mortality in low-risk scenarios, there were marked discrepancies in intermediate- or high-risk scenarios. In these cases, patients tended to be overly optimistic and harbored similar expectations to the lower-risk scenarios, whereas their physicians were more appropriately guarded about the likely outcome. Evidence also suggests, however, that most patients are unaware that their expectations about prognosis often vary from that of their oncologists.

**HOW DOES PROGNOSTIC UNDERSTANDING IMPACT DECISION-MAKING?**

Patients’ prognostic understanding plays an important role in their medical decision-making. Patients who overestimate their likelihood of survival or cure are also more likely to pursue aggressive interventions at the end of life. Other evidence suggests that patients’ understanding of prognosis is associated with their willingness to undergo chemotherapy. For example, in a study of 56 patients with lung or prostate cancer compared with a control group consisting of 20 clinic nurses and radiation technology, investigators used interviews to explore the association between treatment toxicities, associated outcome improvements, and willingness to undergo treatment. There was much variability in willingness to undergo difficult treatments to prolong survival, with patients being much more willing to do so than clinic staff. In addition, there was a clear relationship between expected outcome improvements and willingness to tolerate difficult side effects.

Another study used a hypothetical treatment scenario to demonstrate this relationship. Investigators asked 73 patients with lung cancer and 120 patients without cancer to rate their willingness to undergo various intensities of treatment. Patients were also asked to state the minimum benefit that would make a treatment acceptable. When cure was offered as a possibility, many more respondents expressed willingness to undergo treatment. Similarly, evidence from an interview study suggests that many patients with a history of lung cancer did not actually receive the treatment they would have chosen had they fully understood their prognosis and the benefits and risks conferred by palliative-intent

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**PRACTICAL APPLICATIONS**

- Ensuring that patients have an accurate understanding of their prognosis is necessary to ensure informed decision-making in cancer care.
- Evidence shows that many people with advanced cancer report an inaccurate perception of their prognosis.
- Patients’ prognostic understanding has a great impact on their treatment choices, particularly regarding care at the end of life.
- Novel immunotherapies and genome-targeted treatments, which yield exceptional responses in a small proportion of patients, are further complicating oncologists’ ability to formulate and communicate prognoses to patients with advanced disease.
- Existing approaches to improving patient-clinician communication in oncology are inadequate to accommodate different levels of skill and aptitude among practicing oncologists.
chemotherapies. Other evidence shows that patients who report a more accurate understanding of their prognosis are less likely to receive aggressive therapies at the end of life.

This brief review of published evidence highlights the need for improvements in patients’ overall understanding of their illness, and it suggests that informed decision-making may not actually be occurring frequently. One approach to this problem is for clinicians to discuss prognosis more often and openly. Indeed, evidence suggests that many oncologists simply do not communicate a prognosis, or instead provide an optimistic prognostic estimate to their patients. Although some clinicians report concern that a more accurate disclosure may be upsetting to patients with a poor prognosis, evidence suggests that even those who are upset by learning about their poor prognosis are no less likely to want to know this information. Other evidence demonstrates that when clinicians disclose a prognosis, their patients are more likely to have an accurate understanding of their life expectancy, with no harm to the patients’ emotional well-being or the patient-doctor relationship.

Further research is needed in this area, as a recent analysis points to a slight decrement in patients’ quality of life and mood among those who fully understand their illness. This effect appears to be buffered among patients who adopt active coping strategies. Regardless, these concerns are not sufficient justification for withholding prognostic information from patients and families.

In the sections that follow, we review and discuss emerging issues in prognosis-related communication, including those related to the growing prognostic uncertainty associated with novel therapies and the minority of patients who will achieve an exceptional response to these treatments. Thereafter, we highlight evidence that oncologist-specific factors may contribute to patients’ inaccurate prognostic understanding and thus receipt of overly intensive treatments at the end of life, and suggest potential approaches to improve patient-clinician communication.

EXCEPTIONAL RESPONDERS, HOPE, AND PROGNOSTICATION: MAKING A TOUGH PROBLEM EVEN TOUGHER

The availability of novel, efficacious treatments is changing the landscape of cancer therapeutics and dramatically improving prognosis in a subset of patients with advanced disease. As oncologists, it is gratifying and exciting to administer therapies such as immune checkpoint inhibitors to patients who previously had a prognosis of less than 1 year, and occasionally to see their cancer remain quiescent for many years. Although it is exciting to read manuscripts describing prolonged responses and the tail-at-the-end-of-the curve with immune checkpoint inhibitors, this excitement pales in comparison with the experience of actually witnessing these incredible outcomes when they occur.

A recent case highlights the immense satisfaction and remarkable outcomes sometimes associated with these novel therapies. Karen is a 46-year-old woman with metastatic non–small cell lung cancer whose health was deteriorating rapidly after failure of multiple lines of chemotherapy. We started preparing her to communicate her death with her 7-year-old son when, after months of waiting for insurance approval, we were able to administer nivolumab. Karen had a rapid and complete response, with resolution of her cancer-related symptoms and no immune-related side effects. She is alive and well, and off cancer-directed therapy 3 years later. It is truly exhilarating to witness the sudden improvement of a young person who is dying, with high quality years added to life that simply would not have been attained prior to the availability of this therapy.

Although this case illustrates an exceptional responder, unfortunately, many patients do not respond to immune checkpoint inhibitors, or have underlying health conditions, or experience toxicities that prohibit administration of immune checkpoint inhibitors. Thus, although oncologists who witness cases like Karen’s appropriately feel quite hopeful about the role these therapies can play for patients with advanced cancer, we must balance this optimism with the reality that most patients will not be so exceptional. As oncologists, we have always been responsible for communicating difficult information to patients about their illness, prognosis, and the possible outcomes with therapy. However, the availability of novel therapies and the perception of a more uncertain prognosis that they may create, is making the difficult task of discussing prognosis with patients even more challenging.

There are several reasons why the availability of these novel therapies is making the already tough problem of communicating prognosis more complex. In the case of immune checkpoint inhibitors, there is still a great deal of uncertainty about who will respond to and, indeed, who should receive these agents. In contrast to the use of targeted therapy in patients with defined genetic mutations, such as the use of first-line alectinib in patients with ALK translocations in which the response rate is over 80%, response to immune checkpoint inhibitors is much more unpredictable, even in patients who express the PD-L1 biomarker. For example, in the randomized trial that led to the U.S. Food and Drug Administration (FDA) approval of first-line pembrolizumab for patients with metastatic non–small cell lung cancer, only 30% of potentially eligible patients had sufficient PD-L1 expression to qualify for the study. Even in this population, less than half of the participants achieved a response to pembrolizumab. Although better described in patients with melanoma, a subset of patients who do respond to immune checkpoint inhibitors experience prolonged responses, leading to much discussion about the tails on the survival curves and the possibility of cure. Though these therapies can be effective in patients with low or no PD-L1 expression, the majority of patients who do not express this
biomarker will not respond to immune checkpoint inhibitors, although this varies depending on the tumor type.\textsuperscript{27,28} Thus, although patients may have a cancer type that is eligible to be treated with an immune checkpoint inhibitor (if FDA-approved), it remains unclear which patients will respond, and, of those who do respond, it remains unclear which responses will be exceptional.

There is also a lack of consensus about which patients with comorbid disease are eligible to receive immune checkpoint inhibitors. The toxicities associated with checkpoint inhibitors lead to substantial concerns about administering these treatments to patients, especially to those with underlying autoimmune diseases. Data demonstrate that autoimmune diseases, such as rheumatoid arthritis, may be exacerbated during therapy with checkpoint inhibitors.\textsuperscript{29} Yet, no clear recommendations exist regarding which patients with autoimmune diseases are at risk, or the degree of severity which contraindicates these treatments. Our anecdotal experience is that great variation exists among clinicians in their comfort and willingness to administer immune checkpoint inhibitors to patients with underlying autoimmune disease. In addition to comorbid disease, there are few available data to guide clinicians on administering therapies in patients with poor functional and performance status.\textsuperscript{30}

Although oncologists generally modify their treatment of older patients with marked comorbid disease and refrain from administering chemotherapy to patients with a poor performance status, questions remain about whether they should administer checkpoint inhibitors to very elderly or ill patients. A recent medical record review of patients treated with PD-1 inhibitors demonstrated low response rates and survival in patients with a poor performance status.\textsuperscript{31} This uncertainty about which patients are truly good candidates for immune checkpoint inhibitors further complicates communication about these treatments with patients and their families.

Another challenging situation that occurs more commonly with immune checkpoint inhibitors is when exceptional responders experience toxicities that limit further administration.\textsuperscript{32,33} A recent case highlights the difficulty of this scenario. John was an 82-year-old man whose wife had recently died from pancreatic cancer when he was diagnosed with metastatic non–small cell lung cancer. His perception of chemotherapy was quite negative based upon his wife’s experience, so he was elated when his PD-L1 testing came back at 80%. After two cycles of pembrolizumab, his cancer shrank by approximately 75%, and he experienced marked clinical benefit. Unfortunately, when he arrived in clinic for his planned third cycle of treatment, he had grade 4 elevations in his transaminases. His transaminases improved with prolonged high-dose steroids, and, 5 months after receiving his last dose of pembrolizumab, his cancer remains stable without growth. Although data suggest that he may have a prolonged response despite discontinuing pembrolizumab after only two cycles, he has experienced a great deal of distress about his treatment plan after his cancer grows in the future.\textsuperscript{33} Oncologists occasionally must discontinue targeted therapy or chemotherapy because of toxicity in patients who are having excellent responses, however, this may be a more frequent occurrence with immune checkpoint inhibitors. Thus, oncologists may more often be in the position of supporting patients who must discontinue an effective and life-prolonging therapy because of toxicity.

This greater uncertainty about who will respond to immune checkpoint inhibitors and for how long, as well as which patients can safely receive treatment, makes communicating with patients and their families about prognosis even more difficult and complex. In contrast to alectinib, which is known to work quite well in most patients with metastatic non–small cell lung cancer harboring an ALK translocation, or dacarbazine, which is known to work quite poorly in most patients with metastatic melanoma, at this time we do not have reliable means to predict who will respond to immune checkpoint inhibitors and how well they will work in a given patient.\textsuperscript{34} Physicians are most comfortable when they can provide guidance to patients based upon accurate estimates of benefit and risk. The struggle to communicate effectively with patients and their families is magnified by greater degrees of uncertainty when they must interject the conversations with frequent qualifications of “maybe” or “possibly.”\textsuperscript{35,36} Importantly, the strategies that we must use to communicate with patients and families about the risks, benefits, and possible outcomes of treatment have not changed. These techniques are well outlined in a recent ASCO consensus guideline on patient-clinician communication, and include techniques like “mixed framing,” such as best/worse/most likely outcome.\textsuperscript{37-39} However, it is essential that oncologists do not simply remember and refer to the exceptional responders, like Karen, when engaging in conversations with their patients about prognosis with immune checkpoint inhibitors, and instead express hope balanced with all of the possible outcomes of treatment. In the next section, we discuss oncologists’ communication of prognosis in greater detail, including potential approaches to improving patients’ prognostic understanding to enable them to make goal-concordant decisions about their cancer and end of life care.

**PROGNOSIS-RELATED COMMUNICATION WITH PATIENTS WITH ADVANCED CANCER**

Evidence shows that a substantial proportion of the nearly 600,000 patients who die of cancer each year in the United States experience inadequate or low-quality communication from clinicians. Such poor-quality patient-clinician communication contributes to lower-quality end-of-life experiences, including late receipt of chemotherapy, late referral to hospice, and a lower likelihood of dying at home, the preferred place of death for most Americans. ASCO and the National Quality Forum both advocate for less-intensive medical interventions in the last month of life for patients with cancer.\textsuperscript{40-42} Despite these recommendations, care intensity remains high at the end of life for many patients with advanced cancer\textsuperscript{43} and, in the last 4 weeks of life, health care use and associated expenses often rise.\textsuperscript{44,45}
Although the underlying causes of over-treatment of patients with cancer at the end of life are both complex and multifarious, we contend that the principal modifiable factor is the quality of patient-clinician communication experienced by patients with incurable cancer. Although communication is an issue throughout the trajectory of their illness, most important is the transitional period between the ambulatory phase and the terminal phase of cancer.\textsuperscript{46-49} Multiple studies highlight the persistence of inadequate patient-clinician communication with patients with advanced cancer.\textsuperscript{50,51} Another important body of research shows a strong association between patient-clinician communication and patients’ prognostic understanding and decision-making, suggesting that the quality or effectiveness of communication can have a real impact on the care patients receive at the end of life.\textsuperscript{5} We have already highlighted that patients do indeed want to know about their prognoses, even when the news is not good, and that they want to know about options for care at the end of life.\textsuperscript{15,52} Such communication is associated with patients’ receipt of higher-quality care near death.\textsuperscript{51,53} In addition, evidence shows a link between greater prognostic understanding and decreased preferences for more intensive treatment at the end of life.\textsuperscript{11}

**WHAT ONCOLOGISTS TEND TO DO AND WHY**

Several studies examine the underlying reasons why oncologists avoid communication about prognosis and end-of-life care. Some oncologists worry that, by sharing prognostic information, they will make patients needlessly hopeless or upset, and/or that patients will view them less favorably as a result.\textsuperscript{5,52} However, studies show that patients with serious illness do not lose hope, suffer, or die sooner as a result of end-of-life discussions.\textsuperscript{54-56} Other factors which may contribute to lower engagement in prognosis-related communication include the complexity of balancing hope and accurate information, variable information preferences among patients (and over time within individual patients), and prognostic inaccuracy or uncertainty. One qualitative study examining the barriers to high-quality prognosis-related communication grouped the barriers into: (1) oncologist-related barriers (personal bond, emotional discomfort), (2) patient-related barriers (patient characteristics, diversity, language barriers), and (3) family-related barriers (differential belief in or acceptance of provided prognostic information).\textsuperscript{57}

Because a full review of all of the complex factors that contribute to lower-quality prognosis-related communication is beyond the scope of this article, we choose to focus on oncologist-specific factors. We suggest that oncologists’ experience and comfort with managing patients’ reactions to negative information is a centrally important barrier that contributes substantially to the lack of prognosis-related communication described in the literature.

A large body of evidence suggests that roughly one-quarter to one-third of oncologists avoid or engage rarely in prognosis related communication, or lack skills/aptitude in this area. For example, in the largest study done to date among patients with cancer receiving palliative chemotherapy, patients reported that prognosis was discussed by medical oncologists in only 39% of cases.\textsuperscript{47} In a longitudinal study of hospitalized patients for whom death was believed imminent, 62% of families reported that the attending physician never discussed the possibility of death with them, and that no one discussed the possibility of death with the patient in 39% of cases.\textsuperscript{48} In a review of 37 studies about prognostic awareness, 75% of patients were found to be unaware of their poor prognosis.\textsuperscript{5} Similarly, when nurses were surveyed about their observations of the oncologists with whom they worked, 26% of oncology nurses disagreed or strongly disagreed that their physicians were skilled at prognosis-related communication; 30% of nurses felt that oncologists rarely/never addressed end-of-life issues early in the course of their illness, and 33% of nurses agreed that, when patients did not appear to understand their prognosis, it was because oncologists had not fully discussed it.\textsuperscript{58}

Some of the barriers that contribute to this omission of prognosis-related communication are generalizable to all interpersonal interactions. For instance, Maynard describes social norms that make the delivery of bad news a “dis-preferred” social action. These social interaction norms bias physicians to avoid or delay bad news, or to attempt to qualify or mitigate the news. Lamont found that, even when patients specifically requested information regarding prognosis, physicians only provided frank estimates 37% of the time.\textsuperscript{17} Observational studies suggest that doctors avoid discussion of the emotional and social impact of patients’ problems because of their own distress or because of a perception that they did not have the time to do so adequately. This negative emotional reaction to patients’ distress has been found to negatively affect doctors themselves and, in turn, tended to increase patients’ distress.\textsuperscript{59} Fear of not being able to handle patients’ distress adequately, or that disclosure of negative news will have a detrimental effect on their patients, are major factors in physicians’ reluctance to discuss emotional functioning with patients.\textsuperscript{60}

**POTENTIAL SOLUTIONS**

Could communication skills training help oncologists who are reluctant to engage in prognosis-related communication? A systematic review of communication skills training for cancer care professionals concluded that communication skills training programs are useful for health professionals working in cancer care.\textsuperscript{61} Such programs are associated with improvements in communication skills, knowledge and confidence, changes in attitudes, and satisfaction among health care professionals. Importantly, however, the authors found no evidence of a change in physicians’ abilities to detect patient distress. Evidence is mixed regarding whether physicians who may lack aptitude for complex interpersonal communication can improve with skills training interventions.\textsuperscript{62-65} For example, one study found that physicians with low “identification indices” somehow suppress expression of verbal and vocal cues by patients.\textsuperscript{66} It is unclear whether this can be remedied with skills-based training. In another
recent study, oncologists who participated in a 1-hour didactic training on depressive disorders in patients with cancer were better able to identify depressive symptoms thereafter.64

Perhaps we must admit that oncologists are not all equally skilled at complex communication. Despite this deficit, high-quality communication may be the single most important determinant of appropriate and values-concordant end-of-life care for patients with advanced cancer. If we were to think of oncologists as roughly fitting into three equal communication groups (highly skilled, moderately skilled, and lower skilled), it is clear that each of these groups requires a different approach for intervention. Highly skilled oncologists need organizational support to continue their excellent practice. Examples of organizational support might include practice models that encourage and reward time spent engaging in end-of-life care planning and establishing goals of care at the end of life. In addition, such highly skilled oncologists might serve as mentors or role models within their own spheres of influence, training and assisting their colleagues. Moderately skilled oncologists may comprise the group most likely to benefit from targeted skills training programs, of which several high-quality examples have already been developed (e.g., OncoTalk).65 However, lower-skilled oncologists may be less likely to benefit from skills training.66 For this group of oncologists, efforts to improve their patients’ end-of-life care outcomes might productively be redirected toward programs that supplement their primary cancer care at the end of life, instead of directly attempting to improve their ability to communicate effectively. Examples of such interventions include pairing oncologists with skilled oncology nurses,68 use of palliative care and hospice consultation teams,69 prehospice and care management programs,70 and advance directives completion efforts, as well as models for facilitating structured end-of-life conversations, such as those found in Respecting Choices,71,72 and advanced illness coordinated care programs.73

CONCLUSION

In summary, high-quality patient-clinician communication about prognosis is an essential component of effective cancer care, and is a necessary condition for ensuring that patients make informed decisions about their cancer and end-of-life care. Evidence shows that many patients with advanced cancer fundamentally misunderstand or overestimate their prognosis. These misperceptions adversely impact patients’ decision-making and increase the likelihood that they will receive end-of-life care that is not concordant with their wishes and values. Unfortunately, novel therapies are complicating this already complex problem by making it more difficult for clinicians to estimate and communicate prognosis, as we currently lack reliable tools to predict which patients will achieve exceptional responses. Evidence shows that a substantial minority of oncologists avoids discussions about prognosis, or communicate overly optimistic estimates, a problem which warrants further attention. Although communication skills training interventions have shown some promise in improving oncologists’ communication about prognosis, these programs are only one part of a more comprehensive approach that is needed to meaningfully improve patient-clinician communication, informed decision-making, and care delivery at the end of life.

References


Cognitive Changes in Cancer Survivors

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OVERVIEW

Advances in cancer treatments have led to substantially improved survival for patients with cancer. However, many patients experience changes in cognition as a side effect of both cancer and cancer treatment. This occurs with both central nervous system (CNS) tumors and non-CNS tumors and in both children and adults. Studies of patients with non-CNS cancer have shown that cancer-related cognitive impairment (CRCI), which can include changes in memory, executive function, attention, and processing speed, occurs in up to 30% of patients prior to any treatment and in up to 75% of patients during treatment. A subset of patients with non-CNS and CNS cancer appear to be at higher risk for CRCI, so much research has gone into identifying who is vulnerable. Risk factors for CRCI in adults include cognitive reserve, age, genetic factors, and ethnicity; risk factors for children include genetic factors, female sex, younger age at diagnosis, chemotherapy dose, and both dose and field size for radiation. Although the field has made substantial strides in understanding and treating CRCI, more research is still needed to improve outcomes for both pediatric and adult cancer survivors.

ADULTS WITH NON–CENTRAL NERVOUS SYSTEM TUMORS

Surgery and Prechemotherapy-Related Cognitive Change

Although there has been substantial interest in cognitive decline after cancer treatment, cognitive impairment has been found in patients with cancers outside the CNS following surgery and prior to receipt of any systemic treatment. Wefel et al demonstrated that prior to receiving systemic therapy, 33% of women in a breast cancer cohort exhibited cognitive impairment. In 2008, Ahles et al found that prior to receipt of adjuvant therapy, patients with stage I to III breast cancers performed significantly worse on reaction time tests compared with healthy controls (p = .005). Additionally, patients with stage I to III breast cancers were notably more likely to have lower than expected cognitive performance scores, compared with patients with stage 0 breast cancer and healthy controls. This has been shown in other types of cancer as well. Vardy et al demonstrated that 43% of patients with colorectal cancer had impairment on neurocognitive testing prior to receipt of adjuvant therapy compared with 15% of healthy controls. Yao et al also showed evidence of executive dysfunction in patients with breast cancer prior to receipt of either surgery or chemotherapy. The evidence that there are changes in cognition prior to receipt of any treatment continues to increase, although the mechanism is still under investigation.

Longitudinal Impact of Chemotherapy Exposure on Cognitive Function

Most of the studies to date on CRCI among patients with non-CNS disease have focused on the cognitive impact of chemotherapy, and many studies have been performed with the breast cancer population. The reported frequency of post-treatment cognitive changes varies substantially with the population evaluated, specific measurement tools used, and definitions of impairment or cognitive change. The majority of trials do show cognitive decline from pre- to postchemotherapy, although some have not shown any effect. Findings have shown that patients present with...
subtle cognitive deficits across multiple domains, including several aspects of memory, executive function, concentration, attention, and processing speed rather than frank dementia.5,10-23 A meta-analysis showed that when data from 17 trials were combined, there was a notable decline of moderate magnitude in cognitive functioning at 6 months or greater time since completion of chemotherapy compared with healthy controls or from prechemotherapy baseline. In the studies examined in the meta-analysis, the majority of the deficits were in verbal and visuospatial ability.29 In 2013, Collins et al10 performed a study that noted a dose-response relationship between chemotherapy exposure and cognitive decline. There is often a lack of correlation between patient-reported cognitive complaints and deficits on neuropsychological testing.21,31,32 Patient-reported cognitive complaints are associated with affective distress and other reported symptoms, and patient-reported cognitive dysfunction may be a manifestation of these symptoms rather than an indicator of cognitive decline.33 Alternatively, patients who are aware of their cognitive decline may be more prone to experience distress. Clinicians must fully evaluate all potential contributing and mediating factors of cognitive decline. It is also possible that standard neuropsychological testing may not capture the real-world problems noted by patients. One of the largest longitudinal studies of perceived CRCI to date from Janelins et al34 showed that 45.2% of patients with breast cancer complained of cognitive decline after receipt of chemotherapy compared with 10.4% of healthy age-matched controls. This decline persisted 6 months after receipt of chemotherapy for 36.5% of patients with breast cancer and 13.6% of healthy controls.34

Long-term Postchemotherapy-Related Cognitive Changes
Cognitive decline after chemotherapy can persist long term. Koppelman et al35 evaluated 196 patients with breast cancer treated with cyclophosphamide/methotrexate/fluorouracil at more than 20 years after treatment. Compared with a control population, cancer survivors performed worse in verbal memory, processing speed, executive function, and psychomotor speed.35 Wefel et al21 also showed progressive cognitive decline for patients with breast cancer evaluated 7.7 months after chemotherapy. In their study, 71% of patients showed acute and late cognitive decline, and 61% of patients performed worse on the late evaluation compared with evaluation during or right after chemotherapy.23 However, some studies have suggested that changes can be reversible. Collins et al13 showed that cognitive effects from chemotherapy largely resolved after 1 year; however, their control group consisted of patients receiving endocrine therapy, which can also adversely affect cognition. Additionally, in the study by Ahles et al10 the negative impact of chemotherapy on verbal ability resolved over time, although this was not true of decrease in processing speed. Jansen et al17 also noted substantial improvement in domains affected by chemotherapy 6 months after completion of treatment.

Studies of Cancer-Related Cognitive Impairment With Exposure to Endocrine Therapy
Multiple studies suggest that hormonal therapy for both men with prostate cancer and women with breast cancer can have an impact on cognition.36-38 A meta-analysis of patients with prostate cancer treated with androgen-deprivation therapy showed that patients performed worse on visuomotor tasks compared with either their pre–androgen-deprivation therapy baseline or healthy controls.38 Several trials have shown cognitive effects for women receiving hormonal therapy as well. Schilder et al39 performed a trial comparing performance on neuropsychological testing for postmenopausal patients with breast cancer receiving tamoxifen and exemestane to that of healthy controls. They found that patients who received tamoxifen for 1 year performed significantly worse on verbal (p < .01) and executive function (p = .01) tests compared with healthy controls, although this was not true for patients who received exemestane.39 Ahles et al10 compared patients with breast cancer receiving tamoxifen but no chemotherapy to patients receiving neither treatment. Patients treated with tamoxifen performed worse than healthy controls on processing speed and verbal memory, whereas patients not treated with tamoxifen did not differ from healthy controls.10 Castellon et al41 evaluated neurocognitive outcomes for patients who received adjuvant chemotherapy and tamoxifen. Patients who received chemotherapy performed worse in several neurocognitive domains, but patients receiving both tamoxifen and chemotherapy performed the worst.31 Bender et al41 evaluated cognitive impairment in patients with breast cancer who received adjuvant therapy. They found that patients who received chemotherapy alone had deterioration in verbal working memory, whereas patients who received chemotherapy and tamoxifen had deficits in visual memory and verbal working memory.11 Similar deficits were shown by Palmer et al.40 Finally, Hurria et al41 evaluated patients with
breast cancer older than age 60 who received aromatase inhibitor therapy; they found that although there were few changes in neuropsychiatric performance during the time of the study, there were changes in metabolic activity seen on PET most notably in the medial temporal lobes. \(^4\) Several negative studies have also been published. Paganini-Hill et al \(^4\) found that there was little difference on cognitive tests between women who had used tamoxifen for 5 years and never users, but more women who had used tamoxifen reported seeing their physician for memory problems. \(^4\) Additionally, Hermelink et al \(^4\) did not show a negative impact from use of tamoxifen or aromatase inhibitors.

**Demographic and Medical Risk Factors**

Given that only a subset of patients experience persistent cognitive decline, there has been investigation into factors which make patients vulnerable to CRCI. Age is a well-validated risk factor for many cognitive disorders and may also be important in CRCI. \(^4\) Schilder et al \(^4\) showed that tamoxifen use affected more cognitive domains in women older than age 65 versus those younger than 65. Medical conditions that can affect the vasculature, such as diabetes and hypertension, may also play a role. \(^4\) Additionally, cognitive reserve, defined as innate and developed cognitive capacity, can limit the vulnerability of a patient to brain insults. Ahles et al \(^4\) studied the interaction between chemotherapy exposure, cognitive reserve, and age in patients with breast cancer. They found that patients who were older, had lower pretreatment cognitive reserve, and were exposed to chemotherapy performed worse on tests of processing speed. \(^4\) Other host factors that could influence CRCI include education, race, and ethnicity. \(^4\)

It is also possible that psychological factors play a role. Several psychological and symptom clusters may be related to CRCI, including anxiety, depression, sleep disturbances, and fatigue. These factors are often highly correlated with subjective cognitive measures \(^5\); however, the trajectories of changes in symptoms with changes in subjective and objective cognitive outcomes are still not well understood. Additionally, other factors, including post-traumatic stress disorder, may be involved in CRCI, \(^6\) but more research is needed. \(^4\)

**Possible Genetic Risk Factors**

Genetic factors that may affect vulnerability to CRCI include apolipoprotein E (APOE), catechol-O-methyltransferase (COMT), and brain-derived neurotrophic factor (BDNF). APOE is involved in neural plasticity and repair after injury. \(^4\) Ahles et al \(^4\) studied long-term survivors of breast cancer and lymphoma treated with standard-dose chemotherapy and found that patients with at least one E4 allele performed worse on cognitive testing, indicating that patients with this allele may be more vulnerable to CRCI related to chemotherapy treatment. \(^4\) This effect may be mediated by smoking. \(^4\) COMT influences the metabolic breakdown of catecholamines, impacting dopamine levels in the prefrontal cortex. Small et al \(^6\) evaluated patients with the COMT Val158Met single-nucleotide polymorphism (Val allele), a variant that is related to higher enzymatic activity leading to more degradation of dopamine. They found that individuals who are homozygous for the Val allele have lower amounts of dopamine in the frontal cortex compared with those who have the Met allele. They also found that patients with the Val allele had worse performance on cognitive testing after chemotherapy compared with those homozygous for Met. \(^8\) BDNF is a gene involved in neuron growth and repair and is found primarily in the prefrontal cortex and hippocampus. \(^8\) Ng et al \(^8\) evaluated the BDNF Val66Met polymorphism, which has been linked to aberrant sorting of BDNF into secretory vesicles and decreased activity-dependent BDNF secretion, and development of cognitive impairment after chemotherapy. CRCI was measured using patient-reported outcomes. It was found that the BDNF Val66Met polymorphism was associated with significantly lower odds of developing self-perceived cognitive impairment (p = .036). \(^8\) More genetic factors continue to be under investigation.

**Mechanisms**

The mechanism for CRCI is likely multifactorial, and many potential mechanisms have been explored. \(^5\) As in other disease pathologies, mouse models have provided an important avenue for investigation. Potential mechanisms suggested by animal models include (1) inhibition of hippocampal neurogenesis, (2) oxidative damage, (3) white matter damage, (4) decreased hypothalamic-pituitary-adrenal axis activity, and (5) reduced brain vascularization and blood flow. \(^5\) Other possibilities include direct neurotoxicity with damage to neurons or nerve cells from chemotherapy (particularly fluorouracil and methotrexate, which are more likely to cross the blood-brain barrier) or induced hormonal changes from chemotherapy that lead to cognitive change. \(^5\)

Chemotherapy is also associated with increased levels of proinflammatory cytokines in patients treated with chemotherapy for breast cancer, \(^5\) although inflammatory responses vary by chemotherapy regimen. \(^5\) Multiple studies have linked serum inflammatory markers with cognitive performance. In patients with breast cancer receiving chemotherapy, Williams et al \(^5\) found an association between increasing concentrations of soluble tumor necrosis factor receptors I and II and decline in short-term visual memory. In chemotherapy-treated breast cancer survivors, Kesler et al \(^5\) found that interleukin (IL)-6 and tumor necrosis factor-alpha concentrations were elevated in patients with cancer compared with controls. The breast cancer group also had significantly reduced left hippocampal volumes (p = .01) and deficits in verbal memory as measured by the Hopkins Verbal Learning Test (p = .03). \(^5\) Correlations between inflammatory markers and deficits in cognition have also been found in patients with cancer prior to any treatment. In patients with acute myelogenous leukemia and myelodysplastic syndrome, Meyers et al \(^5\) found that increased levels of IL-6 were associated with worse executive function; increased levels of IL-6, IL-1 receptor antagonist, and tumor necrosis factor-alpha were associated with fatigue;
and higher levels of IL-8 were associated with better memory performance. Other mechanisms have also been proposed, and causes of CRCI remain an area of active investigation.

**ADULTS WITH CENTRAL NERVOUS SYSTEM TUMORS**

Tumors of the CNS include primary brain tumors as well as secondary metastases from malignancy elsewhere in the body. Primary brain tumors are relatively rare (1.4% of all cancers) but are generally associated with substantial mortality and morbidity including cognitive dysfunction. Primary brain tumors vary widely in their biologic activity and aggressiveness, with grade I pilocytic astrocytomas representing a surgically curable lesion in contrast to grade IV glioblastoma with a median overall survival time of up to 20.9 months when treated with surgical resection, cranial radiation, chemotherapy, and tumor-treating fields. Treatment approaches for both primary brain and metastatic brain tumors vary based on a number of features, including histology, tumor molecular features, size, location, patient symptoms, and performance status.

**Cancer-Related Cognitive Impairment With Brain Tumors Prior to Treatment**

Both brain tumors and treatments can cause cognitive decline. Anderson et al reported frequent cognitive dysfunction in patients with brain tumors but further showed a more diffuse and subtle profile of cognitive deficits compared with matched patients with stroke. Cognitive dysfunction is associated with reduced health-related quality of life and functional independence.

**Risk Factors for Cancer-Related Cognitive Impairment With Brain Tumors Prior to Treatment**

There are many clinical factors that can affect the degree of neurocognitive impairment in patients with brain tumors. These factors include lesion size and location, tumor histology, cognitive reserve, and ability to function prior to illness. Patients with more malignant disease show evidence of greater cognitive dysfunction and lower neural network efficiency. In patients with brain metastases, cognitive dysfunction is more strongly associated with the volume of tumor burden than the number of metastases.

In an effort to identify genetic risk factors for cognitive impairment for patients with brain tumors, Liu et al studied 10,967 single-nucleotide polymorphisms (SNPs) among 580 genes involving inflammatory, metabolism, and DNA repair pathways in 233 patients with newly diagnosed glioma. They evaluated associations between SNPs in each of these pathways with processing speed and executive function domains. They reported a linear relationship between neurocognitive impairment and the number of at-risk SNPs in these pathways. The strongest associations were between processing speed and the *insulin receptor substrate-1* rs6725330 SNP and between executive function and *nitrous oxide synthase 1* rs11611788 and *IL-6* rs1912124 SNPs. This is consistent with the link between inflammatory markers seen in patients with CRCI in non-CNS tumors. Liu et al also reported associations between DNA repair pathway genes and neurocognitive function in patients with brain tumors.

**Cancer-Related Cognitive Impairment With Central Nervous System Surgical Resection**

In general, cognitive deficits associated with the tumor and surgical resection correspond to known brain-behavior relationships, with greater deficits on verbally mediated tasks when the dominant hemisphere is involved and greater deficits on visual-spatial tasks when the nondominant hemisphere is involved. Surgery may either improve or worsen cognitive function; however, predicting these outcomes is clinically challenging. For example, 60% of patients with left temporal lobe glioma and 40% with right temporal lobe glioma exhibited substantial worsening after surgical resection most commonly in the domains of verbal memory and executive function.

**Cancer-Related Cognitive Impairment With Central Nervous System Brain Radiation**

Brain radiation is correlated with changes in cognition at doses significantly lower than those required to cause necrosis. Chang et al showed that patients with brain metastases who received whole brain radiation therapy along with radiosurgery were notably more likely to have a decline in verbal learning and memory as shown by scores on the Hopkins Verbal Learning Test compared with those receiving radiosurgery alone. Armstrong et al compared patients with low-grade brain tumors who underwent partial brain radiation to those receiving no radiation. They found that semantic memory was specifically affected in patients who underwent radiation, which would indicate parahippocampal and hippocampal involvement, perhaps indicating that these areas are more sensitive to radiation and involved in radiation-induced cognitive decline.

Douw et al evaluated patients with low-grade glioma at a mean of 12 years after initial diagnosis. They evaluated attention, executive function, verbal memory, working memory, psychomotor function, and information processing speed. Seventeen patients (53%) treated with brain radiotherapy developed cognitive deficits in at least five of 18 neuropsychological test parameters compared with four patients (27%) who were radiotherapy naive. White matter hyperintensities and global cortical atrophy were associated with worse cognitive functioning in several domains. Some studies have shown no cognitive decline; for example, Torres et al found that patients with low-grade brain tumors treated with radiation therapy who did not have tumor progression did not have evidence of cognitive decline. However, the totality of published data strongly support a link between radiation and cognitive impairment.

**Impact of Treatment Modality and Risk Factors for Cancer-Related Cognitive Impairment After Cranial Radiation**

The volume of brain treated has been shown to be correlated with the degree of neurocognitive decline, so treatment
modalities such as intensity-modulated radiation therapy, stereotactic radiation therapy, and proton radiation therapy have been developed to help minimize dose to the normal brain. Stereotactic radiation therapy and stereotactic radiosurgery imply the use of technologies to improve targeting accuracy and allow radiation to be given in larger doses per fraction, thus allowing radiation to be given in fewer fractions. Stereotactic radiation allows a reduction in the radiation dose to the normal brain, so it is commonly used for both metastases and benign tumors.80 Chang et al76 evaluated neurocognition in patients treated with stereotactic radiosurgery versus whole brain radiation therapy along with stereotactic radiosurgery. They found that patients treated with whole brain radiation therapy plus stereotactic radiosurgery were at greater risk of notable decline in learning and memory at 4 months after treatment.76 Intensity-modulated radiation therapy using conventional fractionation utilizes computer-based planning and image guidance to decrease the radiation dose to normal structures and can improve radiation side effects. It is commonly used in partial brain radiation. Proton radiotherapy, which has a minimal exit dose compared with photon radiotherapy, can also potentially improve the conformality of radiation plans and reduce dose to normal tissue.81

The brain is very sensitive to the dose of radiation per fraction, with larger doses causing greater damage to normal tissue.82 Given the larger doses per fraction used in stereotactic radiosurgery, radiation necrosis is a commonly reported complication and is commonly surrounded by edema, which can be either symptomatic or asymptomatic. Edema can also occur in the absence of necrosis.80 The risk of complications increases with the target size in stereotactic radiation.83 With either stereotactic or conventional radiation therapy, neurologic deficits can occur as a result of either direct radiation damage to a critical structure or compression from edema.

Many of the studies investigating the effect of radiation therapy on cognition do not specifically look at dose-volume exposure of neuroanatomic targets within the brain, but more studies are now being done in this area. Peiffer et al84 retrospectively evaluated neuroanatomic structures that received 10, 40, and 60 Gy in patients who were treated with partial brain radiation and found that dose to specific neuroanatomic structures predicted global cognitive outcome at doses greater than 60 Gy. The hippocampus has been of particular interest, and radiotherapy dose to bilateral hippocampi is associated with verbal memory decline.85 Further, for patients treated with whole brain radiation therapy, hippocampal avoidance showed verbal memory preservation in a recent phase II trial.86 More studies are needed to evaluate whether dose to specific neuroanatomic structures influences cognitive outcomes.

**Mechanisms of Cancer-Related Cognitive Impairment After Cranial Radiation**

Classic radiation biology categorized the CNS as late-responding tissue, meaning that the dose per fraction would have a notable impact on radiation injury and the injury would be seen at a delayed time. Recovery of neural tissue was predicted to be very limited by this model. However, animal studies have shown that there is substantial repair of neural tissue occurring up to 3 years after radiation.83

Clinically, radiation toxicity can be divided into acute, early delayed, and late phases. In the acute phase, there is acute inflammation with production of cytokines and blood-brain barrier disruption. In the early delayed phase, there is thought to be transient demyelination. Late neurotoxicity occurs at least 3 months after radiation exposure, and the results can be highly variable. There may be radiation necrosis, which can occur in areas that received high doses of greater than 60 Gy. One consistent manifestation of late radiation damage is white matter damage.82 Cognitive deficits can occur as a result of either direct radiation damage to a critical structure or compression from edema. There may also be chronic inflammatory changes. Radiation biology studies have shown that damage from radiation is a complex process, involving changes in the microenvironment and infiltration of immune cells. Mouse models have shown a multiphasic response to radiation with delayed immune cell infiltration into the brain.87

**Treatment of Cancer-Related Cognitive Impairment in Adults**

Regardless of whether it is related to the cancer or the treatment, CRCI can decrease quality of life, interfere with a patient’s ability to work and contribute to society, and lead to poor compliance with treatment and clinical follow-up.88,89 Eighty percent of patients with chronic illness including cancer said they would not have chosen a treatment if they had known it would affect their cognitive ability,90 and cancer survivors who self-report cognitive difficulties indicate a negative impact on their quality of life.91 Thus, concerns about cognitive problems should be evaluated and addressed by the treating physician and psychologists. Measures recommended by the International Cancer and Cognition Task Force for assessment of adults include the Hopkins Verbal Learning and Memory Test—Revised, the Controlled Oral Word Association, and the Trail Making Test. These can be used by clinicians and researchers to assess individual time points or evaluate changes over time from prior to treatment into survivorship. Referrals to social workers and neuropsychologists may also be needed.

Interventions focus on cognitive training, cognitive rehabilitation, physical activity, and pharmaceuticals. Cognitive training is a behavioral method of training based on models of neuroplasticity (cognitive skills can be improved using drills to exercise the brain).92 Cognitive rehabilitation involves learning compensatory strategies to minimize the impact from acquired cognitive deficits with the goal of improving function with everyday tasks.92 New and innovative ways of providing cognitive rehabilitation are under investigation. Recently, Bray et al93 published a study using a web-based cognitive rehabilitation program for cancer survivors reporting CRCI after chemotherapy. The program was compared with
standard care. The results were promising, showing less perceived cognitive impairment in the treated group immediately after intervention and 6 months later. Physical activity is another option for treatment of CRCI. The general recommendation for breast cancer survivors is 150 minutes per week of moderate to vigorous physical activity, given evidence from clinical trials that exercise can improve persistent symptoms such as fatigue and pain and can enhance quality of life and body image. Pharmacologic interventions include methylphenidate and modafinil, both of which combat fatigue and promote wakefulness to improve cognitive performance. For methylphenidate, the results have been mixed, with some trials showing improvement in cognition and others showing no improvement. Results of a meta-analysis of five trials showed overall improvement in cancer-related fatigue, although they showed no impact on depression or cognition. For modafinil, some early studies have shown promise. However, in a multicenter, double-blind placebo-controlled crossover trial by Boele et al, patients with a primary brain tumor showed no improvement in fatigue, mood, or cognition compared with placebo. Specifically, for patients who receive brain radiation, the impact of donepezil and memantine on cognition has been studied. The phase III study showed no improvement in a cognitive composite score with the use of donepezil for patients who underwent partial or whole brain radiation. Brown et al studied memantine for patients who received whole brain radiation. Although the primary endpoint was not met, it was found that memantine delayed time to cognitive decline.

**PEDIATRIC PATIENTS**

Research into neurocognitive late effects of childhood cancer began in the 1980s and initially focused on patients with brain tumors and/or exposure to cranial radiation. Although there is a clear impact on neurocognitive function for these patients, research has also shown that chemotherapy also affects neurocognitive outcomes but potentially in more subtle ways.

**Cancer-Related Cognitive Impairment With Cranial Radiation for Central Nervous System Tumors**

CNS malignancies represent 30% of childhood tumors. The treatment often involves multiple modalities, including surgery, radiation, and systemic therapy. Over the last decade, dramatic improvements in treatments have resulted in improved progression-free survival. However, as many as one-half of pediatric patients with brain tumors will develop progressive neurocognitive decline, which means that many of these patients are left with substantial cognitive side effects.

For pediatric patients, cranial radiation has a role for treatment of primary brain tumors and, until recently, was used for CNS prophylaxis for certain disease. Unfortunately, there is substantial evidence that cranial radiation leads to cognitive deficits. Jankovic et al evaluated children who had received cranial radiation to a dose of 18 Gy and found that there was a substantial decline in full scale intelligence quotient (IQ) scores. Younger age at time of radiation was associated with lower full scale IQ scores as well as longer time since initial diagnosis. Krull et al evaluated long-term survivors of acute lymphoblastic leukemia who received cranial radiation at either 18 or 24 Gy. Patients also received intrathecal methotrexate. Patients were evaluated initially 1 to 10 years after therapy and then were subsequently re-evaluated in adulthood. On the initial evaluation, survivors had lower performance IQ but not verbal IQ scores. On the subsequent testing, there was a substantial decline in verbal IQ scores, suggesting a progressive effect from treatment even after 10 years. For patients with pediatric CNS tumors, Brinkman et al evaluated 224 survivors of CNS tumors a median time from diagnosis of 18 years. Radiation records were reviewed and survivors were divided into those who received focal radiation, craniospinal radiation, or no cranial radiation. The investigators reported that 11% of survivors who did not receive cranial radiation had impairment in long-term memory, compared with 25% of patients treated with focal radiation therapy and 36% of patients treated with craniospinal radiation. Craniospinal radiation was correlated with the greatest risk of severe neurocognitive impairment, with a relative risk of 2.7 for intelligence, 3.96 for academics, 1.54 for attention, and 1.44 for memory. Other factors associated with cognitive impairment included history of hydrocephalus with shunt placement, which was associated with risk of impaired intelligence and memory, as well as seizures, which were associated with impaired academics, attention, and memory.

Radiation dose, volume and site of brain radiated, and age at time of radiation can all affect the overall outcome. For pediatric patients, cranial radiation doses of 36 Gy are associated with worse neuropsychological outcomes at 3 years after treatment compared with cranial radiation doses of 23.4 Gy. Additionally, radiation therapy to a dose of 35 Gy reduced processing speed more than 25 Gy doses. Mabbott et al reviewed 36 children treated for posterior fossa tumors with cranial radiation. They found that younger age at time of radiation predicted poor reading ability and lower parent rating of academic achievement. Jalali et al showed that cranial radiation doses greater than or equal to 54 Gy had a significantly higher risk of decrease in full scale IQ by greater than 10%. They also showed that higher volume of the left temporal lobe receiving greater than 43 Gy was significantly associated with a decrease in full scale IQ (p = .04). Female sex is associated with a higher risk of adverse neurocognitive outcomes. Certain areas of the brain are known to be more sensitive to radiation. The developing hippocampus is very sensitive to both chemotherapy and cranial radiation therapy in pediatric cancers. Both chemotherapy and cranial radiation are linked to altered hippocampal function and smaller hippocampal volumes. For pediatric brain tumor survivors, the size of hippocampal subfields was correlated with performance on verbal memory testing. In the pediatric population, many practitioners
now use proton radiotherapy to improve conformality of plans and reduce late side effects as much as possible.116

Cancer-Related Cognitive Impairment With Chemotherapy for Non–Central Nervous System Tumors

Current treatments for childhood cancers have begun to favor chemotherapy without radiation whenever possible. Given this, there have been more opportunities for studies in the last 10 years to focus on neurocognitive side effects of chemotherapy alone. Kannellopoulos et al117 evaluated 112 adult survivors of childhood acute lymphoblastic leukemia who were treated with chemotherapy only. They found that survivors performed poorly on tests of processing speed, executive function, and working memory. There was no impairment in general intellectual ability.117 Survivors of childhood osteosarcoma, typically treated with adjuvant high-dose intravenous methotrexate, have also been shown to have cognitive deficits in reading skills, attention, memory, and processing speed.118

The most common deficits seen with chemotherapy alone are deficits in visual processing,119,120 visual-motor functioning,119,121,122 and attention and executive functioning.123-125 Between 25% and 33% of children show some evidence of neurocognitive decline regardless of the specific chemotherapy protocol.126,127 Girls generally present with worse deficits than boys,126,128 and children treated at younger ages generally have worse deficits.129 As in adults, there is a dose-response relationship between cognitive changes and dose of chemotherapy. In survivors of childhood acute lymphoblastic leukemia treated with high-dose methotrexate, there was a correlation between higher doses of methotrexate and worsened deficits in attention,124 as well as executive function and processing speed.130

Demographic and Medical Factors

Several studies have been published that help to show which pediatric cancer survivors are more vulnerable to CRCI related to chemotherapy. Patients who develop acute leukoencephalopathy during chemotherapy have worse cognitive deficits in organization and initiation as well as reduced white matter integrity within the frontostriatal tract.131 Additionally, pediatric patients often develop chronic health problems during long-term survival,132 which can also influence cognition. Twenty to thirty percent of long-term survivors with chronic health conditions were noted to complain of decreases in task efficiency and memory.133

Genetic Factors

As in adults, there is variability in the severity of neurocognitive changes seen in pediatric patients with cancer. In addition to the risk factors discussed above, there may be genetics that modulate this effect. Barahmani et al134 evaluated the relationship between the glutathione S-transferase enzyme genes, responsible for detoxification of alkylating and platinum-containing agents as well as oxygen-free radicals, and neurotoxic effects in children with medulloblastoma. The majority of the patients in this study were treated with craniospinal radiation as well as high-dose platinum chemotherapy. If patients had at least one null GSTM1 or GSTT1 genotype, they recorded lower performance on general, verbal, and nonverbal intelligence.134 In patients with medulloblastoma, the GSTM1 null genotype was also associated with self-report of anxiety, depression, and global distress scores.135

The COMT gene has also been found to modulate CRCI in children treated for brain tumors. In survivors of nonmedulloblastoma brain tumors, patients with the Met allele were found to perform better on an executive function task.136 Finally, there are reports associating specific methylene tetrahydrofolate reductase variants with both increased risk of attention deficit hyperactivity disorder and reduced attention and executive function in survivors of acute lymphoblastic leukemia.137-139

Treatment for Pediatric Patients

For pediatric patients, the Children’s Oncology Group140 has published “Guidelines for Identification of, Advocacy for, and Intervention in Neurocognitive Problems in Survivors of Childhood Cancer.” They recommend that neuropsychological function be assessed before, during, or shortly after the completion of treatment. This will provide a baseline should the child’s performance begin to decline. Difficulty with prolonged school absences or trouble at school should trigger neuropsychological evaluation. Developmental status should be assessed annually by the primary health care provider. Subtle changes in executive function, reasoning, and time management may not manifest until children transition into middle and high school. At all times, ongoing communication between parents and teachers is encouraged. The authors report that there is preliminary evidence that methylphenidate can be used in some survivors with attention and learning difficulties, but this requires further trials.140

CONCLUSION

CRI in both pediatric and adult cancer survivors is an important issue that is receiving increasing attention. Cognitive impairment is frequent and expected for patients with CNS tumors, but it has also been found in patients with non-CNS cancer before treatment and following chemotherapy. Many cancer therapies have nonspecific, off-target toxicities that can adversely affect cognition. A subset of patients with non-CNS and CNS cancer appear to be at higher risk for CRCI, so much research has gone into identifying who is vulnerable. Risk factors for CRCI in adults include cognitive reserve, age, genetic factors, and ethnicity; risk factors for children include genetic factors, female sex, younger age at diagnosis, chemotherapy dose, and both dose and field size for radiation. Although substantial strides have been made in understanding and treating CRCI, more research is still needed to improve outcomes for both pediatric and adult cancer survivors.
References


Pain Management in the Era of the Opioid Crisis

Eduardo Bruera, MD, and Egidio Del Fabbro, MD

The vast majority of patients diagnosed with cancer will have episodes of acute or chronic pain.¹ ² Not all those episodes require opioid management. However, opioids will be necessary in almost all patients at some point for the management of acute or chronic pain. Table 1 summarizes common pain syndromes among patients with cancer that frequently or rarely require systemic opioid treatment.

Opioids are highly effective analgesics, and all physicians involved in the treatment of cancer patients should be familiar with the most common types and dosages of opioid analgesics as well as the management of their most common side effects.³

Figure 1 summarizes the complex effects of opioids on different central nervous system regions. Systemic opioids bind to mu receptors along the nociceptive pathway and reduce neuronal activity and pain perception at the somatosensory cortex. Unfortunately, opioids also bind to mu receptors anywhere in the body where they are available. As a result, patients experience mu-related side effects such as constipation and somnolence. Mu receptors are located also along the limbic system, and they are therefore able to produce considerable reward, especially in patients with large concentrations of mu receptors in those regions. There is a slow development of tolerance and hyperalgesia along the nociceptive pathway and a much faster reduction of the reward effect centrally. This rapid loss of the reward effect is associated with the increased activity of dysphoric pathways that are not mu related. Patients who are at higher risk for the development of substance use disorders will increase opioid intake in an effort to restore the reward, followed by once again rapid loss of such effect.

Approximately 80% of patients receiving opioids for the management of cancer pain will adhere to the opioids as prescribed and will have no major difficulties with dose reduction and even discontinuation if the pain syndrome resolves.⁴ The remaining 20% are at risk for behaviors consistent with the nonmedical use of the opioid analgesic (also defined as aberrant behaviors) or will ultimately develop substance use disorders.

There are risk factors associated with the development of opioid dependence among patients with advanced cancer. Among these, the most common risk factor is a history of alcoholism. Positive screening results for risk of alcoholism in the general population are approximately 8%, but it is considerably higher among patients with cancer.⁵ ⁷ Parsons et al⁸ found positive results of risk screening in 100 of 598 patients with advanced cancer (17%). One possible explanation for this higher frequency of alcoholism is that alcohol is an etiologic factor for many cancers.

Other risk factors such as a history of dependence on other drugs are less frequent among patients with cancer.⁹ ¹⁰ Unfortunately, the majority of patients treated with opioids for the management of cancer pain do not undergo regular screening for the risk of alcoholism or a history of drug use, therefore, there is considerable underdiagnosis of these problems. A number of studies for more than 20 years have documented that extremely simple tools such as the CAGE-AID questionnaire (Sidebar 1) can detect high risk for alcoholism much better than the regular oncology and even supportive and palliative care medical encounter. Tools such as the CAGE-AID questionnaire⁹ and the Screener and Opioid Assessment for Patients With Pain⁹ can be very useful in assisting in the determination of risk for nonmedical opioid use in the routine oncology setting. One challenge is the appropriate documentation of concerns of nonmedical opioid use. In a recent study 76 of 432 patients were diagnosed as using opioids nonmedically by a palliative medicine specialist (18%), but only 15 of those patients (4%) had documentation in their medical records.¹⁰ Appropriate documentation of concerns regarding nonmedical use of opioids will greatly improve the early diagnosis and early management of this complication of cancer pain management. In patients in whom screening tools have not been used, a history of smoking can be helpful. Among 300 consecutive patients with advanced cancer, the rates of CAGE-positive status among never smokers, former smokers, and current smokers were 3%, 12%, and 42%, respectively. Similarly, rates of history of street drug use were 3%, 16%, and 33%, respectively.¹¹

Patients with higher risk for nonmedical opioid use are more likely to engage in behaviors such as those summarized in Sidebar 2. When these behaviors are detected, the physician should immediately suspect nonmedical opioid use and have in place a care plan for the management of this complication. Among the measures that can be implemented is the...

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use of urinary drug screening. In a supportive and palliative care program, 61 of 1,058 patients (6%) underwent urinary drug screening because of suspected nonmedical opioid use, and 33 (54%) had abnormal results.11

The majority of patients with nonmedical use of opioids obtained the drugs from family and friends. Patients with cancer have limited knowledge of the safe use, storage, and disposal of opioids.12 Among 300 patients with advanced cancer, 26% reported unsafe use by sharing or losing opioids, and 19% stored opioids in plain sight.12 The administration of a simple brochure with educational material resulted in considerable improvements in storage, use, and disposal behaviors.13

After the completion of curative radiation therapy to the head and neck, 44 of 70 patients were still receiving opioids more than 3 months later, and 23 of 70 patients (33%) were on opioids more than 6 months after the completion of treatment.14 Forty-four percent of patients who were unable to stop opioids were CAGE positive, compared with 12% of patients who were able to stop opioids (p = .014). The median number of days receiving opioids was 261 for CAGE-positive patients and 93 for CAGE-negative patients (p = .008).

Concerns about the use of opioids have had an impact on overall opioid use for patients with cancer by their medical oncology teams. Between 2010 and 2015, the median morphine-equivalent opioid dose of patients upon the moment of referral to the Supportive Care Center at The University of Texas MD Anderson Cancer Center decreased from 78 to 40 mg/day (p = .001).15

WHAT DO ALL THESE FINDINGS MEAN TO YOUR ONCOLOGY PRACTICE?

Approximately 20% of patients with cancer who need opioids for the management of cancer-related pain are at risk for the development of nonmedical opioid use or a substance abuse disorder. The routine clinical encounter misses approximately 80% of patients who are at this increased risk. Extremely simple and free bedside validated tools allow for effective, universal screening for those patients who may be at a higher risk of nonmedical opioid use. Figure 2 proposes an algorithm for the screening and follow-up of these patients.

THE TREATMENT OF PATIENTS WITH CANCER-RELATED PAIN AND NONMEDICAL OPIOID USE

Patients who are identified as having histories of addiction or being at risk for nonmedical opioid use may be challenging for clinicians, especially those patients on high opioid doses or complex regimens or those exhibiting nonmedical opioid-related behavior. These patients would benefit from referral to palliative care or pain-specialist teams for structured treatment that includes documentation of treatment agreements, intermittent urine drug screening, frequent

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**TABLE 1. Pain Syndromes in Patients With Cancer**

<table>
<thead>
<tr>
<th>Opioids Required Frequently</th>
<th>Opioids Required Infrequently</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic pain due to advanced cancer</td>
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<td>Acute muscular-skeletal pain syndromes (e.g., low back pain)</td>
</tr>
<tr>
<td>Radiation-chemotherapy-induced mucositis</td>
<td>Minor dental/diagnostic procedures</td>
</tr>
</tbody>
</table>

**PRACTICAL APPLICATIONS**

- Recognize patients at higher risk for nonmedical opioid use.
- Learn about screening for chemical coping risk.
- Diagnose nonmedical opioid use.
- Manage nonmedical opioid use in the clinical oncology setting.
- Understand clinical criteria for referral to supportive and palliative care teams.

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**SIDEBAR 1. CAGE-AID Questionnaire**

- Have you ever felt that you should Cut down on your drinking (or drugs)?
- Have you ever been Annoyed by people criticizing your drinking (or drugs)?
- Have you ever felt bad or Guilty about your drinking (or drugs)?
- Have you ever had a drink first thing in the morning or a drink (or drugs) to get rid of a hangover (Eye opener)?

Note: Patients scoring 2 or higher have approximately 80% risk for alcohol use or drug use disorder.

**SIDEBAR 2. Behaviors Suggestive of Nonmedical (Aberrant) Opioid Use**

- Frequent unscheduled clinic visits or phone calls for refills
- Self-escalation of opioid dose
- Frequent emergency room visits for opioids
- Edmonton Symptom Assessment Scale pain intensity 10/10 with all other symptoms 0/10
- Seeking opioids from multiple physicians (“doctor shopping”)
- Request for specific opioid
- Reports of stolen/lost opioids
- Family member expressing concern over the patient’s opioid use
- Obtaining opioids from nonmedical sources, stealing, selling
- Requesting opioids for insomnia or anxiety
- Abnormal urinary drug screen
- Discrepancy in pill counts

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visits with shorter intervals, and restricted quantities of “breakthrough” opioids. These specialist teams encounter high-risk patients more frequently and have more resources and experience in managing complex clinical issues using an interdisciplinary approach. The concurrent strategies that may be used by these teams are outlined in the following discussion.

Interdisciplinary Approach
Because patients with aberrant opioid-related behavior may have multiple underlying biomedical, psychosocial, financial, and legal issues, the expertise of multiple providers working in concert is likely the most effective approach. Depending on resources, specialized interdisciplinary teams may consist of a variable combination that includes physician, nurse, psychologist, social worker, and pharmacist. An innovative program within the supportive care clinic at MD Anderson implemented a compassionate high-alert team to address nonmedical opioid-related behavior in patients with cancer. The team has a full complement of multidisciplinary members, plus patient advocacy and risk management or security representatives if legal or safety concerns seem imminent. The team rather than any individual provider prepares a plan before patient arrival and then collectively meets with the patient, providing support in a nonjudgmental manner with an emphasis on the need for patient and family safety. This specialized team intervention decreased the median number of nonmedical use behaviors from 3 to 0.4 per month (p < .001) and the morphine-equivalent daily dose (MEDD) from 165 to 112 mg/day (p = .018), without increasing pain severity compared with a control group. Another National Cancer Institute cancer center with an interdisciplinary palliative care team found ambulatory patients who have no evidence of disease are less likely to respond with reductions in pain scores compared with those with active cancer.

Past studies revealed that patients with aberrant behavior and chemical coping are more likely to receive a higher MEDD for pain control and are more likely to experience opioid side effects. Besides chemical coping and diversion, clinicians should be aware of other factors that increase pain perception or expression, including somatization, delirium, hyperalgesia or allodynia, opioid tolerance, drug interactions, and neuropathic pain. Most studies related to aberrant behavior or chemical coping are from the outpatient setting, and a very different approach may be required for inpatients. Pain perception and expression may be altered for a number of reasons: patients may be more ill in the hospital, they may be more likely to experience cognitive impairment and delirium, and they may be on intravenous patient-controlled analgesia. Few studies have reported outcomes on inpatients at risk for chemical coping or with a history of aberrant behavior delivering their own breakthrough doses by patient-controlled analgesia. A couple of case reports have noted the potential for harm occurring in patients with advanced cancer on patient-controlled analgesia, including unnecessary dose escalation and opioid induced neurotoxic side effects such as delirium. Palliative care units with robust interdisciplinary teams may be especially well placed to manage patients with histories of aberrant behavior or chemical coping on intravenous opioids, but more research is needed in this regard.

Patient and Family Education Regarding Opioid Management
From the outset, patients and their families should understand that opioids are not the sole focus of therapy and will be combined with other pharmacological agents as well as nonpharmacological modalities. Standardized documentation should be provided, including pain treatment agreements along with informed consent detailing information about the potential risks and benefits associated with opioid

FIGURE 1. Opioid Effects on the Nociceptive and Non-Nociceptive Pathways

Abbreviation: MOR, mu opioid receptor.
therapy, possible adverse effects, and education on opioid safety and disposal strategies.12,13

Comorbid Psychiatric Conditions and Psychological Interventions

Patients should be evaluated and treated for any underlying comorbid psychiatric conditions, and comanagement with psychiatry should be considered. A study of patients with co-occurring opioid use disorder and chronic noncancer pain reported a lifetime prevalence of more than 90% for having comorbid psychiatric conditions, such as anxiety and mood disorders. Similarly, there is a risk that some oncology patients could use opioids in a maladaptive manner to cope with the stress of advanced cancer and mental health conditions that may emerge during their disease.

Several nonpharmacologic interventions have been shown to be effective in managing noncancer-related pain and may be useful in decreasing opioid use. These include multidisciplinary biopsychosocial rehabilitation,25 cognitive behavioral therapy, mindfulness-based therapy,26 relaxation techniques, biofeedback, and distraction techniques.27 Patients should receive brief motivational interviewing with an objective, nonjudgmental, and empathic style that includes personalized feedback, particularly about markers of risk or harm. Although studies are not universally positive, and research in patients with cancer is lacking,28 brief motivational interviewing has been successful in managing patients with alcohol misuse.29

Nonopioid and Adjuvant Analgesics

In patients at risk for opioid misuse and mild pain, nonopioid and adjuvant analgesics should be considered. Some pain syndromes such as chemotherapy-induced peripheral neuropathy are known to be particularly resistant to opioids. Pain due to chemotherapy-induced peripheral neuropathy warrants duloxetine as a first-line therapy and consideration of other nonopioids, such as gabapentin and nortriptyline, rather than opioids. Similarly, providing there are no contraindications, nonsteroidal anti-inflammatory drugs30 and acetaminophen should be considered as options for bone pain or their opioid-sparing potential. Opioids should be considered only in patients with moderate to severe pain that is
unresponsive to nonopioid therapies, because this population-derived benefit from opioids in randomized trials.31

Opioid Type and Formulation
On the basis of studies using administrative data and healthy volunteers, immediate-release oral opioids32 or rapidly administered intravenous opioids33 may increase the risk for opioid misuse.34 A large Veterans Affairs study of 750 overdose deaths found that patients with cancer-related pain were less likely to overdose than those with noncancer conditions, but among those patients with cancer, the use of only as-needed immediate-release opioids increased the risk for overdose death compared with those taking extended-release or scheduled immediate-release opioids.35 Reassuringly, preliminary evidence from this study suggested that patients with cancer receiving palliative care were less likely to overdose. Given the potential risk with rapid-onset opioids, extended-release formulations or long-acting opioid analgesics such as buprenorphine or methadone should be considered in those patients with established chronic cancer-related pain and aberrant behavior. Methadone and buprenorphine are approved for treating opioid addiction and coupled with psychosocial support are the current standard of care for reducing illicit opioid use, relapse risk, and overdoses, while improving social function.36 It is unclear whether they have similar benefits for patients with cancer by mitigating or preventing opioid misuse, although both medications are known to be effective for cancer pain.37,38 The goal to manufacture tamper-proof oral formulations that cannot be injected or inhaled has merit because these routes are often associated with misuse because of their rewarding effects. However, these formulations can still be misused orally16 and are expensive, and their overall clinical impact on decreasing opioid misuse has not yet been determined. The future holds promise for development of nonaddictive opioids, targeting nonopioid pain pathways, or using medications such as kappa agonists that counteract the aversive effects of opioid withdrawal.39

Selective Use of Naloxone
A nonrandomized observational study of patients with chronic pain reported that coprescribing naloxone, a short-acting opioid antagonist, reduced emergency department visits without causing an increase in prescribed opioid doses.39 Despite the potential for benefit, there are still many unanswered issues, including demonstration of improved outcomes and decreased health care use. Current recommendations regarding MEMP and the need for concomitant naloxone prescription vary (e.g., Virginia recommends consideration of naloxone for patients with MEDD ≥ 120 per day, while the Centers for Disease Control and Prevention recommend considering offering naloxone for patients with MEDD ≥ 50 per day). Most regulations are consistent in excluding cancer-related pain, but for chronic noncancer pain, there is agreement that a history of drug overdose, a history of substance use disorder, or concurrent use of benzodiazepines34 warrants a naloxone prescription. Most states also allow pharmacists to dispense or distribute naloxone without a patient-specific prescription from another health professional. Although excluded from regulations, patients with cancer and histories of overdose or addiction should be considered for prescribed intranasal naloxone with instructions for administration by relatives and caregivers.

CONCLUSIONS
The vast majority of patients with cancer need opioids for the management of pain. Oncologists can safely and effectively manage the majority of these patients. Universal screening for risk factors and careful monitoring for the emergence of nonmedical opioid use behaviors help decide on the need to refer patients for specialized care.

References
The field of psychosocial oncology is a young discipline with a rapidly expanding evidence base. Over the past few decades, several lines of research have established that psychosocial problems, such as anxiety, depression, post-traumatic stress, fatigue, sexual dysfunction, and cognitive complaints, are common and consequential in patients with cancer. The word “distress” was chosen deliberately to capture a broad concept; consequently, distress screening is meant to function as an initial step in the more targeted evaluation of the source(s) of the patient’s distress. In 2015, the American College of Surgeons’ Commission on Cancer mandated psychosocial distress screening as part of their accreditation process. Similar screening requirements are in place internationally, including in Canada, where screening for distress is endorsed as the sixth vital sign and a standard of care that must be met by any Canadian health care organization providing cancer services that seeks to be accredited. Over the past few years, cancer centers around the world have been exploring optimum ways to implement and evaluate distress screening initiatives. This paper presents three approaches to distress screening implementation: (1) a model that incorporates the importance of shared values, perceived benefits, and relevant outcomes in the implementation of distress management protocols; (2) a Canadian knowledge translation application to distress screening, including triage considerations and interventions; and (3) a novel approach to distress management via the use of a mobile application to manage post-traumatic stress symptoms. In closing, future opportunities and challenges associated with the emergence of technology will be discussed.

The National Comprehensive Cancer Network defines distress as “a multifactorial unpleasant experience of a psychological (i.e., cognitive, behavioral, emotional), social, spiritual and/or physical nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. It extends along a continuum, ranging from common, normal feelings of vulnerability, sadness, and fears to problems that can be disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis.” The ultimate goal of systematic distress screening in oncology settings is to identify and address otherwise unmet biopsychosocial needs.

In contrast to more narrowly defined constructs, like depression, the word distress was chosen deliberately to capture a broader concept. Consequently, distress screening is meant to function as an initial step in the more targeted evaluation of the source or sources of the patient’s distress. Consider two patients who each score above a trigger threshold for distress screening. The first patient is a 29-year-old woman with breast cancer who had been doing well until she developed severe panic attacks during radiation therapy. The second patient is a 55-year-old man with colon cancer who is moderately troubled by peripheral neuropathy that interferes with his piano playing, financial concerns since taking a leave from work, and the fact that he has to pay for parking at the cancer hospital. Both patients
may have similar scores on a distress screening instrument but clearly require quite different clinical and programmatic responses to their distress.

In 2015, the American College of Surgeons’ Commission on Cancer mandated psychosocial distress screening as part of their accreditation process. Similar screening requirements are in place internationally. In Canada, Screening for Distress is endorsed as the sixth vital sign, and it is a standard of care that must be met by any Canadian health care organization providing cancer services that seeks to be accredited. Over the past few years, cancer centers around the world have been exploring optimum ways to implement and evaluate distress screening initiatives.

In the United States, neither the Commission on Cancer nor any other cancer-related organizations specify which screening instrument should be used to identify patients who are distressed. Consequently, a wide variety of tools and screening strategies have been used by clinicians and researchers. The most frequently used instrument is the National Comprehensive Cancer Network Distress Thermometer (DT), a 0 to 10 point visual analog scale that is coupled with a problem checklist of 35 sources of distress. The last several years have brought efforts to validate the DT in different oncology settings around the world and in diverse patient populations. Other cancer centers use validated depression scales, such as the Patient Health Questionnaire (PHQ-9), or customized surveys administered by paper or as part of an electronic tablet–based screening system.

Given the overall morbidity and mortality associated with cancer, the prevalence of psychosocial distress in oncology settings is not particularly surprising. What has been less expected is the emerging evidence of increased mortality associated with at least one expression of psychosocial distress: depression.

At the 2017 ASCO Annual Meeting, Basch and colleagues reported positive results from a trial of 766 patients with cancer undergoing treatment of advanced solid tumors who were randomly assigned to a web-based system to ask about several patient-reported outcomes (symptoms commonly associated with distress). Patients who reported their symptoms online in real time so that they could be addressed by clinicians benefited from a 5-month survival advantage compared with patients who did not use the web-based system to report their symptoms. This compelling study represents the potential benefits of prospective monitoring of distress (for both quality of life and survival).

Detailed accounts of the history and rationale for screening have been extensively addressed in other publications. Similarly, issues related to the relative advantages and disadvantages of different distress screening instruments are beyond the scope of this article. Instead, we will focus on more practical aspects of implementing distress management protocols. For example, how should psychosocial oncology clinical teams organize themselves to respond to patients who are distressed? What are best practices for matching the patient’s source of distress with appropriate interventions within or outside of a particular oncology setting? We also address effective strategies for the uptake and modification of distress screening. Specifically, we will present three approaches to distress screening implementation: (1) a model that incorporates the importance of shared values, perceived benefits, and relevant outcomes in the implementation of distress management protocols; (2) a Canadian distress knowledge translation application to distress screening; and (3) a novel approach to distress management via the use of a mobile application to manage post-traumatic stress symptoms and discussion of future opportunities and challenges associated with the emergence of technology in this sphere (Sidebar 1).

PRACTICAL APPLICATIONS

• Distress management requires screening, tailored education, referral, and follow-up.
• Personalized care requires addressing the diverse psychosocial needs of the cancer community.
• Clinicians must prioritize the value of screening to the patients and families, because those who see benefit in distress management protocols will be more likely to participate.
• Modifying clinical practice is challenging—the best distress screening programs use knowledge translation strategies to support clinicians in their oncology practice.
• Technology can facilitate personalized medicine by providing self-management interventions, such as mobile applications and web-based programs.

SIDEBAR 1. General Principles From a Decade of Experience With Distress Screening in Oncology Settings

• Screening alone (i.e., without a coherent referral and/or intervention program) is not helpful.
• The specific tool matters less than how the results are responded to.
• Timing matters (e.g., screening on first visit results in false-positive findings).
• Screening can be used for programmatic evaluation (e.g., which clinics are seeing more distress and what kind of distress is most common in each clinic).
• Uncovering more distress than the system has capacity for is both a real and perceived problem.
• What happens after screening is where the real impact is felt within a system.
• A thoughtful and institution-specific triage system is key.
• There are different needs based on men and women, different ages, different cancer types, different timing, and different screening tools used.
IMPLEMENTATION AND REFERRALS

The dramatic increase in and implementation of distress screening have not necessarily resulted in effective ways to implement such complex processes. Because distress screening is inherently a clinical function, all too often clinicians may not recognize that they already possess the requisite skills to engage key stakeholders in developing highly successful distress screening programs. In fact, we have argued that comprehensive distress screening is the connective tissue of the health care system.22

Implementation in its simplest form can be defined as strategically applying specific behaviors that lead to self-reinforcing, sustained, and desired outcomes. For comprehensive distress screening programs, this means sensitizing patients and families to problems endemic to cancer and its treatment, identifying specific problems triaged to individuals and/or services, and providing real-time information tailored to the patient’s needs (with documentation in the health record). The potential impact of distress screening is robust and can, when done correctly, reverberate throughout the entire system.

The introduction of this kind of systemic change requires considerable effort. In addition, programs that attempt to transform culture also must be relentlessly sustained over time for implementation to be integrated as part of standard of care. Most of all, there needs to be a realistic engagement of key stakeholders: treating physicians (especially), institutional leadership, and related health care staff (e.g., nurses, social workers, and physician assistants). Although an in-depth discussion of culture change is beyond the scope of this article, there are a number of easily accessible resources available to the interested reader.23

Despite personal insecurities about program development, many health care professionals do possess the requisite clinical skills to engage colleagues (managing up/across/down) and quickly show the benefits of distress screening. Here, we share one straightforward approach to multilevel engagement that has led to cultural transformation in a number of settings: shared values, perceived benefits, and relevant outcomes.24

IMPLEMENTATION: SHARED VALUES, PERCEIVED BENEFITS, AND RELEVANT OUTCOMES

Unrealistic workloads, lack of time, understaffing, financial pressures, and space limitations are common in cancer settings. The convergence of and interactions between these realities result in emotionally charged and exhausting environments that include patients, families, faculty, and staff (and by extension, their own family members, who may be affected by proxy). Any dissemination plan for distress screening must take into account the mindset and unabridged realities of those key stakeholders who must be engaged, motivated, and whenever possible, inspired. Harsh judgements about colleagues or delusions about the setting usually result in delays or failure to launch. These obstacles must be addressed to sustain a fledgling program. Programs are, by practical definition, packages of people, ideas, and resources aspiring to a common outcome.

The first step in the implementation process is commonly a vision of one person or a small group of motivated (by desire or directive) individuals who see the initial vision (desired outcome) as a starting point for a much wider discussion. Essential to any new program is the ability to engage and inspire others to perceive the program as directly relevant to them. One such approach is to make manifest shared values, perceived benefits, and relevant outcomes. This is achieved by (1) meeting with and gaining the perspectives of key stakeholders and (2) gaining information from other sources who are personally knowledgeable about the stakeholders who you seek to engage. Shared values refers to those aspirational core beliefs that drive behaviors about how one should engage others in the world. Perceived benefits are much more personal and relate more to the here and now, answering the questions: why should I care about what you want me to do, and what do I get out of this? Relevant outcomes are the agreed on desired measurable results that build on the foundation of the already established values and benefits. This process is easy to use, practical, and readily adapted to other audiences: physicians, patients, family members, colleagues, business administrators, clinic managers, etc. Figure 1 shows how one might engage a treating physician to actively support a distress screening program.

DISTRESS SCREENING AS THE CONNECTIVE TISSUE OF THE INSTITUTION: TEAMWORK AND TRIAGE

Distress screening programs have become much more than what was originally envisioned. This has occurred in part because of the emergence of electronic health re-

FIGURE 1. Engaging Treating Physicians for Biopsychosocial Screening Programs

<table>
<thead>
<tr>
<th>Shared Values</th>
<th>Perceived Benefits</th>
<th>Relevant Outcomes</th>
</tr>
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<tbody>
<tr>
<td>Compassion</td>
<td>Protect my time</td>
<td>Higher satisfaction</td>
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<tr>
<td>Competence</td>
<td>Manage non-treatment related obstacles to care</td>
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cords but also, because of robust pressures from patients, family members, and payers, all demanding real-time, efficient, and effective coordination of cancer care. Screening has also impacted how health care professionals work together as teams. Real-time identification of physical and psychological problems, triage to identified professionals and resources, tailored educational materials, data for new program development, and research all benefit from screening programs. One particular unanticipated area where screening has had an impact is in the way that health care providers work together: confronting siloes, challenging turf, and being encouraged to have open and honest communications about what is truly in the best interest of patients and their families, colleagues, and the institution. These are all highly emotionally charged subjects that, in too many circumstances, result in avoidance, superficial conversations, insincerity, and potential for undermining of colleagues and teamwork. The potential negative impact on patient care is obvious. As shown in Figure 2, a supportive care team can work together to define and document areas of clearly defined specific expertise (based on license, institutional sanction, specialized training, and unique abilities) and other clinical areas where blurring is encouraged.

RESPONDING TO BIOPSYCHOSOCIAL SCORES

The purpose of implementing a distress screening program is to understand the patient’s perspective in relation to their physical, emotional, psychological, social, practical, and/or spiritual needs. Distress screening can be considered personalized medicine, because each patient has different needs and services tailored to improve quality of life.

Implementing distress screening is only successful if scores are reviewed and acknowledged by a health care professional in an effective and timely manner with appropriate interventions and follow-up. In Canada, the Edmonton Symptom Assessment System revised scale (ESAS-r) and the Canadian Problem Checklist (CPC) are endorsed by the Canadian Partnership Against Cancer as two screening tools. Evidence-based practice guides have been developed to support the clinical practice of health care professionals in addressing symptom scores identified on the ESAS-r and the CPC. The practice guides and algorithms are available for symptoms identified on the ESAS-r (pain, tiredness/cancer fatigue, drowsiness, nausea, lack of appetite, shortness of breath, depression, and anxiety).

Many practice guides and algorithms support a step care model approach by recognizing the variability and severity of symptoms experienced by patients with cancer. Care

FIGURE 2. Team Work and Triage24

Department of Supportive Care Medicine (DSCM) Clinical Triage

<table>
<thead>
<tr>
<th>Social Work</th>
<th>Psychology</th>
<th>Psychiatry</th>
<th>Supportive Medicine</th>
<th>Spiritual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety/Risk assessment for abuse, suicide, homicide, AMA</td>
<td>Psychoneuropathic management of mental health issues impacting treatment</td>
<td>Assessment &amp; management of altered mental status</td>
<td>Symptom assessment &amp; management</td>
<td>Assessment of spiritual &amp; existential needs &amp; distress</td>
</tr>
<tr>
<td>Pre-transplant psychosocial assessment</td>
<td>Assessment of cognitive &amp; emotional functioning</td>
<td>Pharmacologic treatment of psychiatric disorders</td>
<td>Symptom management for patients with substance use concerns</td>
<td>Spiritual counseling, including grief &amp; bereavement support</td>
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<tr>
<td>Evaluation, support &amp; triage of patient &amp; family coping &amp; distress</td>
<td>Interventions &amp; treatment planning for high acuity behavioral &amp; adherence issues</td>
<td>Acute management of substance use disorders</td>
<td>Prognostication</td>
<td>Interventions for spiritual &amp; moral distress about treatment &amp; end of life decision-making</td>
</tr>
<tr>
<td>Counseling for adjustment to illness &amp; changes in medical status</td>
<td>Psychological techniques for symptom management</td>
<td>Assessment of psychiatric stability for treatment</td>
<td>Initiation of &amp; assistance with goals of care discussions</td>
<td>Spiritual interventions around end of life clinical processes, e.g. DNR, miracle thinking</td>
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<tr>
<td>Interventions to reduce barriers to care</td>
<td>Individual psychotherapy for severe cancer-related distress, e.g. anxiety, depression</td>
<td>Assessment of medical decision-making capacity</td>
<td>Assistance with hospice evaluation &amp; transition</td>
<td>Facilitation of spiritual/religious rituals, sacraments &amp; services</td>
</tr>
<tr>
<td>End-of-life &amp; hospice discussions</td>
<td>Grief &amp; bereavement support</td>
<td>Acute management of suicide &amp; homicide risk</td>
<td>“Aid in Dying” consultation</td>
<td></td>
</tr>
<tr>
<td>Coordination &amp; facilitation of family meetings</td>
<td>Coordination &amp; facilitation of family meetings</td>
<td>Management of actively dying patients</td>
<td>Palliative sedation</td>
<td></td>
</tr>
<tr>
<td>Couples counseling &amp; education (cancer-related)</td>
<td>School program</td>
<td>Palliative sedation</td>
<td></td>
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<tr>
<td>Advance Directives counseling</td>
<td>Assistance with community resources, e.g. financial, mental health, transportation</td>
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<tr>
<td>“Aid in Dying” assessment &amp; counseling</td>
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Abbreviations: AMA, against medical advice; DNR, do not resuscitate.
Adapted with permission from Schnaitmann et al.25
should be delivered in the least restrictive manner and the most economical fashion. For the purpose of this article, the focus is on responding to psychosocial distress.

Fitch’s model (Fig. 3) for service provision and proportion of patients requiring assistance for distress underscores the importance of tailoring services in a way to maximize access to the most appropriate health care professional. A step care model has potential to mitigate the burden placed on psychosocial specialists to address all distress scores (e.g., for anxiety and depression). Based on the model, all patients should be screened and receive information and basic emotional support. When patients are first seen by oncology clinicians, communicating effectively, showing empathy, and providing patient education will ensure that these needs are addressed and may prevent distress scores from escalating. However, if distress scores on a screening report are high, it may require the health care team to have a conversation with the patient to consider a referral to a psychosocial specialist who can assess and provide additional interventions. The same is true for a social worker who may be working with a patient who identifies shortness of breath on the ESAS-r in addition to experiencing anxiety. The social worker may provide some education/interventions to help manage the anxiety and may also refer the patient to the oncologist and/or nurse for additional assessment and intervention for the shortness of breath. In essence, a good biopsychosocial approach to care requires a step care model that supports good interdisciplinary care by the team.

The Canadian Association of Psychosocial Oncology developed a Pan-Canadian Guideline for the screening, assessment, and management of distress, depression, and anxiety in adults with cancer. The algorithms are consistent with Fitch’s model (Fig. 3) of service delivery approach to recognize the importance of routinely screening patients for distress, depression, and anxiety. The algorithms outline when patients should be screened (e.g., at entry into the system/time of diagnosis, critical times in disease and/or treatment process, points of transition for survivorship, time of recurrence, palliative care, and end-of-life care). Each screening program may define different criteria for screening. For example, when we implemented a distress screening program in 14 community hospitals where chemotherapy is delivered closer to home, nurses were asking patients to complete the ESAS-r and the CPC at each cycle of chemotherapy, and some nurses were using their discretion to screen more often to determine if scores were improving.

Good clinical practice to support distress screening requires health care professionals to review the distress scores with the patient and ensure that the scores are accurate. Patients may misinterpret how to complete the symptom report, especially when numerical scales are involved. In our experience with patient satisfaction surveys, we sometimes receive comments from patients wondering why they should complete a report, because it seems that nobody is looking at it. By acknowledging and reviewing the scores with patients, it lets them know that someone is paying attention to their scores, and it reinforces patients’ participation in the management of their symptoms.

It is also important to ask patients what symptom they would like to address today. In our experience, health care professionals often express the concern that patients may have several items identified as a need on a symptom report. There is often limited time in a busy clinic to address all symptoms. By asking the patient what symptom matters most right now, health care professionals can focus their attention on the most pressing need from the patient’s perspective. If more than one symptom cannot be addressed in the clinic appointment, an additional appointment or...
telephone call may be necessary to address the other concerns based on severity of scores. In the algorithm for depression,\textsuperscript{29} this is referred to as a comprehensive assessment that also includes asking questions to understand how distress in interfering with daily life, assessing past history for depression, and assessing for support and risk factors. Based on health care professionals’ scope of practice and/or time available, they may feel comfortable to proceed to a focused assessment or will discuss and recommend to the patient a psychosocial referral to a psychosocial specialist (e.g., psychiatrist, psychologist, social worker, or other) who can proceed with a focused assessment.

For example, the focused assessment may entail using additional patient-reported outcome measures, like the PHQ-9 scale, to ascertain the level of depression. The health care professional will assess for Diagnostic and Statistical Manual of Mental Disorders (DSM-5) depressive symptoms and assess for persistence of symptoms more than 2 weeks (all day, every day). Based on ESAS-r or PHQ-9 scores, the severity of scores are color coded, where green indicates mild distress/depressive symptoms, yellow indicates moderate distress/depressive symptoms plus impairment, and red indicates severe distress/symptoms of severe or major depression.\textsuperscript{29}

The step care model can be followed for all green, yellow, and red scores. For example, measures that can be taken for all patients, regardless of symptom severity, are normalizing cancer distress and providing education (verbal or written) on signs and symptoms of depression and when to seek additional support. All patients can be provided with information about peer-led support groups, self-management tools, and other strategies for exercise, mindfulness, optimal nutrition, etc. In addition to the step care model, additional interventions are recommended for yellow and red scores and can be offered by a psychosocial specialist. Importantly, distress screening programs should have a suicide protocol in place in the event that the patient is at risk of harming oneself and/or other(s).\textsuperscript{29}

The practice guides and algorithms are meant to support the clinical practice of health care professionals working with patients with cancer. Scope of practice is important, and responsibilities to respond to biopsychosocial screening scores may be shared by various members of the interdisciplinary team. It is essential that the role of each member of the team be well understood with service referral pathways. If these are not in place, referrals may not be initiated to psychosocial specialists. In cases where geography may have various members of the team separated on different sites, innovative models of care can be developed, such as telemedicine, to ensure that patients have access to the necessary specialist.\textsuperscript{30}

Finally, modifying clinical practice is challenging for any health care professional. A good distress screening program requires knowledge translation strategies to support clinicians in their clinical practice in an ongoing fashion: academic detailing, case presentations, and didactic presentations followed by group discussions are all strategies that have worked in our experience with distress screening.

\section*{SIDEBAR 2. Implementation Matters: Lessons Learned From Comprehensive Distress Screening}

- Implementation strategies must be reality based; they should begin the process by understanding the shared values, perceived benefits, and desired relevant outcomes of treating physicians and then consider additional stakeholders.
- Plans to manage the realities of time constraints, staffing levels, and available resources are an essential part of the implementation process.
- Conflict and resistance are to be expected, and they are an opportunity for honest and open value-based conversations.
- Programs should encompass the “person in environment” model, and those that focus on only one aspect of care (i.e., psychological problems) will experience greater resistance to uptake.
- Data from screening programs have great potential to inform clinical care, patient education, program development, research, grant writing, and quality improvement.
- Clinicians must prioritize value to the patients and families, because those who see benefit in distress management protocols will be more likely to participate.

Supports for professional development are important for health care professionals to feel confident that they can manage the program, such as keeping current and expanding their competencies to address distress scores and provide evidence-based interventions (Sidebar 2).

\section*{SYMPTOM SELF-MANAGEMENT APPROACHES}

Although distress screening and referrals have been shown to be effective for patients who visit the oncology setting regularly, concern exists for those who may not return to the oncology clinic but have long-term physical and/or psychosocial issues related to the cancer experience. Often, cancer survivors live at a distance from the oncology clinic and are followed up by their general health care professional, who may be less knowledgeable about cancer-related issues. Solutions are critically needed to address the needs of these cancer survivors as well as those who are unable to receive quality cancer care because of limited resources and the increasing cost of services.

Symptom self-management approaches are receiving increased attention because of their scalability and cost-effective platforms. According to Lorig and Holman,\textsuperscript{31} there are five core skills inherent in self-management interventions: problem solving, decision-making, resource use, communication with health care professionals, and task planning or goal setting. Although often introduced by the oncology
clinician, these interventions shift the responsibility of distress management to the cancer survivor, such that they become “active” rather than “passive” participants in their care.

In a recent systematic review, several trials related to self-management in cancer survivors were identified. The six interventions targeted exercise, diet, anxiety, depression, coping, and quality of life outcomes—and all but one study reported substantial results. However, the authors stated that there is a lack of quality studies and consensus around the definition of “self-management.” Therefore, they were unable to draw definitive conclusions as to the impact of the different types of self-management programs on cancer-related outcomes. In addition, they concluded that there is a need for personalized solutions that could be used in the cancer survivors’ daily lives because of the poor sustainability of the interventions.

**CANCER DISTRESS COACH: A SYMPTOM SELF-MANAGEMENT APPLICATION FOR POST-TRAUMATIC STRESS**

Several years ago, a need was identified to develop an application that would address the five self-management components described earlier and facilitate the management of cancer-related post-traumatic stress disorder (PTSD) symptoms. The National Center for PTSD had developed a similar application for their veteran population, and a collaboration was formed with Duke University to revise the application for cancer-specific PTSD. The Cancer Distress Coach (CaDC) application provides education, assessments, resources, and cognitive behavioral therapy (CBT)-based activities related to PTSD symptoms (Fig. 4).

Given our finding that about one in three cancer survivors has recurring PTSD symptoms, such as flashbacks or nightmares related to the diagnosis or treatment; avoidance of reminders, including oncology follow-up appointments; and/or hyperarousal, including sleep difficulties, we developed the CaDC as a tool to be with the survivor in any given moment. For example, we found in a pilot study among 31 cancer survivors that the highest application usage occurred during midnight and 2:00 AM—likely because of the users’ inability to fall or stay asleep. Overall, the application was shown to be effective in reducing PTSD symptoms after 4 weeks of usage.

**SIDEBAR 3. Self-management Components Within the CaDC Application**

1. Problem solving is facilitated through the provision of feedback within the Insights module related to their score on the PTSD Checklist instrument.
2. Decision-making is aided by the Learn module, in which information related to their symptoms and where to get help (i.e., the role of each member of the multidisciplinary team) is displayed to the user.
3. Resource use is encouraged through the Find Support activity; in addition, users are prompted with immediate, toll-free call-in information should they report a high distress level.
4. Communication with health care professionals is enabled by the presentation of assessment feedback within the Insights module that is presented over time in graphical form.
5. Task planning or goal setting.

Spurred by the promising finding from our study, the CaDC was rebuilt using iOS ResearchKit and Android ResearchStack to facilitate research activities (e.g., consent form and data collection are conducted within the application) and allow for an efficient platform for future expansion work. The CaDC application is being studied nationally among cancer survivors and caregivers in a randomized control trial and available as a free download on the AppStore and Google-Play (Sidebar 3).

**FUTURE DIRECTIONS AND CHALLENGES**

Preliminary data from the randomized control trial indicate that the CaDC is effective in helping individuals self-manage their symptoms of post-traumatic stress. We see a promising intervention effect. The mean change in PTSD Checklist score for the CaDC treatment group (mean change, −5.7; standard deviation, 10.0; 17 patients) is different from the mean change for the CaDC attention placebo control group (mean change, 0.6; standard deviation, 12.0; 28 patients).
and is approaching significance (p = .08). In addition, we are seeing a moderate effect size (Cohen’s d = 0.56). Despite these findings, additional work is needed to expand its reach and effectiveness.

To expand population reach, the application was built to be compatible with low socioeconomic status populations (e.g., sixth grade reading level text), and additional funding is being sought to develop a Spanish version. In addition, several requests have been received from investigators and cancer survivors in other countries (e.g., Mexico, Canada, and the United Kingdom) to make the application available within their AppStore and GooglePlay. Given the licensing and research implications, this would require the approval from an Institutional Review Board within each country in addition to finding a sponsor.

There are initiatives underway to enhance the effectiveness of the application. First, the application is being expanded to focus on a broader array of symptoms in support of a specific cancer type. Content will be added to the Learn, Insights, and Activities modules to support the palliative care needs of this population. Second, the research team plans to study the application in a comparative effectiveness trial that compares the efficacy of the application as a standalone intervention versus augmenting the application with two additional interventions. Third, the research team aims to work with Duke software developers to develop an interface to the electronic health record system after the technology is available within EpicCare (Epic Systems, Verona, WI).

Mobile health applications, such as the CaDC, have the potential to enhance reach and facilitate symptom management, thereby transitioning our health care system into a personalized and value-based cancer care environment. However, several challenges and considerations remain: (1) resistance to change and fear that technology will impede clinical workflow; (2) barriers related to cost and lower uptake of smart devices (e.g., tablets and iPhones) among vulnerable populations, such as older survivors and those with lower incomes; and (3) lack of evidence of efficacy among most of the health-related applications available in the AppStore and GooglePlay. Therefore, future research is needed to address these barriers and facilitate the integration of technology into quality cancer care.

CONCLUSION

Many individuals who were diagnosed and treated with cancer experience symptoms, such as anxiety, depression, pain, insomnia, post-traumatic stress, fatigue, sexual dysfunction, and cognitive issues, well into survivorship. Comprehensive biopsychosocial distress screening programs are being implemented internationally as a means to identify survivors who are experiencing cancer-related issues and refer them to appropriate clinicians for follow-up and treatment more and more frequently in real time. Despite the broad implementation of such programs in the clinic, several barriers still exist, such as difficulties in reaching the cancer survivor who no longer visits the clinic regularly for cancer care. An increase in the number of electronic patient-reported outcome systems includes mobile technologies as a means to address some of the barriers. Additional research is needed, such as comparative effectiveness studies that examine the efficacy of various programs and cancer survivor populations.

References


Currently, there are 15.5 million cancer survivors living in the United States. The number of survivors is expected to rise to 26.0 million because of improvements in therapy and an aging population. As cancer survivor numbers increase, there will be an increased burden of long-term side effects, such as cancer treatment–induced bone loss, which is a loss of bone mineral density (BMD) that is strongly associated with fracture risk. These resulting fractures can have serious sequelae, because hip fractures increase mortality by 10% to 20%. Hormonal manipulation resulting in estrogen or androgen deprivation is a therapeutic intervention for many types of malignancies, including breast and prostate cancer. Although the majority of the cancer treatment–induced bone loss literature focuses on aromatase inhibitors (AIs), there are a number of other cancer therapies that can increase the risk of bone loss in patients.

### ALTERATIONS IN BONE METABOLISM

Normally, endogenous gonadotropin-releasing hormone is physiologically released in a pulsatile manner from the hypothalamus and directed to the anterior pituitary gland. Subsequently, luteinizing hormone and follicular stimulating hormone are released from the pituitary. This stimulates testosterone and estrogen production. Estrogen prevents bone loss by influencing the production of numerous proinflammatory cytokines by bone marrow and bone cells. The main consequences of increased cytokine production in the bone microenvironment are increased osteoclast formation, elongation of their lifespan, increased activity of mature osteoclasts, and increased osteoblastic activity. Postmenopausal osteoporosis is characterized by a progressive loss of bone tissue that begins after natural or surgical menopause. In vitro studies have shown the role that androgens play in bone health, including the proliferation and decrease in apoptosis of osteoblasts; mineralization, which is the late differentiation stage of osteoblast; prevention of parathyroid-induced osteoclast formation; and decreased bone resorption activity of osteoclast.

The rate of bone loss in males is less than that in females. The BMD reduction rate at the lumbar spine in normal men is 0.5% neck versus 1.0% in late menopausal women and 2.0% in early menopausal women.

### ANDROGEN-DEPRIVATION THERAPY

Androgen-deprivation therapy (ADT) is the most widely used therapeutic modality in prostate cancer, and it is associated with complications. ADT is the mainstay of initial therapy for systemic disease, whether it is asymptomatic biochemical recurrence (BCR) and prostate-specific antigen rise after definitive localized therapy or overt metastatic disease. Older patients with prostate cancer are more likely to be treated with ADT than other modalities, including watchful waiting, and the use of ADT is increasing. Even in men age 80 and older with low to moderate grade tumors who are asymptomatic from their prostate cancer, ADT use...
increased from 3.7% in 1991 to 30.9% in 1999.12 Because older patients tend to be diagnosed with more indolent cancers and live with prostate cancer as a chronic disease, they experience marked complications from ADT, which get worse over time.9 In some cases, patients discontinue ADT because of side effects, which can cause their prostate cancer to progress.

Although ADT increases survival time for localized prostate cancer,13 its use is associated with numerous adverse events. Patients with prostate cancer on ADT incur a five-to 10-fold greater annual loss of BMD than men of similar age who are not diagnosed with cancer.14-18 Testosterone deficiency caused by ADT results in estrogen deficiency, which contributes to increased bone resorption and decreased bone formation, ultimately leading to decreased BMD.19-22 As a result, men treated with ADT have up to a sevenfold increase in risk of fracture compared with men of the same age who were not treated for prostate cancer,22-24 resulting in a significantly (p < .05) increased mortality rate.25 In addition, total body fat increases in men on ADT, and there is also a loss of lean muscle mass (sarcopenia) on the order of 2% to 5% that occurs shortly after ADT initiation.26-28 Both BMD and muscle loss may contribute to declines in physical performance.29 Older men are at increased risk for falls because of age,30 and the risk of falls may be exacerbated by ADT. Patients with prostate cancer on ADT have up to a fivefold increase in falls compared with prostate cancer survivors not on ADT, contributing to the increased fracture rate.31,32

Agents such as AIs, which block the conversion of androgen into estrogen, are used in the prevention, adjuvant, and metastatic settings for breast cancer. Nearly complete suppression of plasma estrogen levels has been shown consistently with all third generation AIs.33 The estimated lumbar spine BMD loss at 1 year is 2% in AI therapy for postmenopausal women and 7% in AI therapy plus agonists.34

Bone loss in patients with breast cancer as a result of AIs has been well characterized through a number of large phase III clinical trials. The ATAC trial, which compared the efficacy and safety of anastrozole with those of tamoxifen, showed a fracture rate of 11% versus 7.7%, respectively after a median follow up of 68 months. The BIG 1-98 trial, which compared letrozole with tamoxifen, showed a fracture rate of 8.6% versus 5.8% respectively at 51 months (p < .001). The increased fracture rate for letrozole persisted at 5 years with a reported 9.3% versus 6.5% (no p value reported). The International Exemestane Study compared the efficacy and safety of either 5 years of tamoxifen or a switch to exemestane after 2 to 3 years of tamoxifen treatment for a total of 5 years. At a median follow-up of 58 months, the study showed a 7% fracture rate in the exemestane arm and a 5% fracture rate in the tamoxifen arm (p = .01).7

Studies have shown that AI therapy resulted in increases from baseline in all bone turnover markers (e.g., bone-specific alkaline phosphatase, amino terminal propeptide type I, procollagen, and osteocalcin) at all time points.35

### HYPOGONADISM IN NONHORMONE-DEPENDENT MALIGNANCIES

Hypogonadism can occur in cancers that are not hormone dependent and can result from chemotherapeutic agents and radiotherapy.36,37 Chemotherapy-induced ovarian failure is one of the most common causes of hypogonadism in females with nonhormone-dependent malignancies. The effect of chemotherapy on ovarian function depends on the types of chemotherapy and age of the patient, because increased age is a risk factor for ovarian failure.38 Although menstrual function is retained in the majority of patients, they remain at risk for natural menopause at an early age, which increases the likelihood of bone loss.39 Alkylation agents, including cyclophosphamide, are the most likely to cause premature ovarian failure, whereas other agents, such as platinum agents, taxanes, and anthracyclines, carry a lower risk.40,41 Women who experience premature ovarian failure often have rapid loss of BMD with substantial effects observed within 6 months.38 One study of 49 patients with early-stage (stage I/II) premenopausal breast cancer patients receiving chemotherapy found that women with premature ovarian failure lost almost 8% of their BMD in the first 12 months compared to no significant (p > .05) decrease in BMD in women who did not experience ovarian failure.41 Fogelman et al42 examined BMD loss in 96 women treated with a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) or goserelin and found a 6.5% decrease in spinal BMD and a 4.5% decrease in hip BMD at 2-year follow-up. They also reported a higher percentage of BMD loss in women with premature ovarian failure compared with women without ovarian failure, and there was limited recovery of BMD 3 years postdiagnosis. In general, hypogonadism results in BMD loss that is more severe and rapid than BMD loss as a result of AIs and ADT.

Premature ovarian failure as a result of chemotherapy is most common in patients with breast cancer, but it can occur with other cancer sites. Cyclophosphamide significantly increases the risk of hypogonadism in both genders and is used to treat lymphoma, multiple myeloma, leukemia, and ovarian cancer.33-45 Combination chemotherapy regimens are also associated with hypogonadism; bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone results in ovarian failure for more than
one-half of female patients.46,47 Mechlorethamine, vincristine, procarbazine, and prednisone chemotherapy is strongly associated with hypogonadism in both genders after treatment of leukemia, with over 50% having irreversible gonadal toxicity.48,49 Risk of hypogonadism increases with age, because younger patients often regain gonad function.50

Patients with testicular cancer as a result of their hypogonadal state remain at an increased risk for bone loss. Ondrusova et al studied the damage of bone metabolism in testicular cancer survivors. The study evaluated 1,249 patients who were treated for testicular cancer with either orchiectomy (OE; median age at diagnosis, 30 years), OE plus radiation therapy (median age at diagnosis, 34 years), or OE plus chemotherapy (median age at diagnosis, 29 years). The authors concluded there was a higher incidence of osteopenia/osteoporosis in patients with decreased testosterone one levels as compared to those with normal bone mineral density (p < .01). Consistent with other studies, the authors concluded that the type of therapy, including chemotherapy and radiation therapy, did not influence incidence of osteopenia. The incidence of osteoporosis increased with age and was modestly associated with time from surgery, particularly after 10 years, suggesting that declining testosterone levels are causative.51,52

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

Glucocorticoids are commonly used as a supportive agent for a number of cancers, including multiple myeloma, prostate, breast, and hematologic cancers.53 Glucocorticoids are also used in antiemetic regimens, and the ASCO recommends using glucocorticoids for the prevention of nausea and emesis in highly and moderately emetogenic chemotherapies.54 Long-term glucocorticoid use is a known risk factor for bone loss and can result in osteoporotic fractures for up to 30% of long-term users.55,56 However, it remains unclear whether short-term use of glucocorticoids significantly contributes to BMD loss in patients with cancer. One study of 50 female lymphoma patients (26 premenopausal and 24 postmenopausal) found a significant decrease in BMD with glucocorticoid use but only in females with ovarian failure, indicating that glucocorticoids may not significantly contribute to BMD loss.57 The authors believed that it is unlikely that high-dose intermittent glucocorticoid contributed to the lowering of BMD. Because glucocorticoids are often administered in conjunction with other agents known to cause bone loss (hormonal therapies, chemotherapies, and gonadotropin-releasing hormone agonist), it is difficult to tease apart the effect of these drugs on BMD in patients with cancer.

METABOLIC SYNDROME AND ENDOCRINE THERAPY

Other metabolic alterations remain of concern for patients with cancer. Metabolic syndrome is a disorder composed of central obesity, hypertension, insulin resistance, and dyslipidemia.

Body composition changes secondary to menopause. As a result of loss of estrogen, there is an accumulation of central fat. The accumulation of intra-abdominal fat is a risk factor for cardiovascular disease and type 2 diabetes mellitus.58 Clinical trials have reported reversible but substantial increases in total cholesterol.59

The prevalence of metabolic syndrome has also been reported in patients with prostate cancer on ADT. Men who are hypogonadal are at increased risk for central obesity and thus, metabolic alterations. Rezaei et al60 reported the incidence of metabolic syndrome in men (190 patients) on ADT, particularly intermittent type, at 6 and 12 months after treatment. The incidence rates were 6.8% and 14.7%, respectively. The investigators also found that patients had higher overall incidence of of abdominal obesity (p < .001), hypertriglyceridemia (p < .001) in their 6- and 12-month follow-up and hyperglycemia (p < .001) at 12 months.60 Various investigators have reported an increased risk of diabetes or higher levels of fasting serum glucose levels on ADT. The duration of ADT was directly related to the severity of these metabolic abnormalities, because similar findings were not reported in patients on shorter-duration ADT. Basaria et al studied the influence of ADT and hyperglycemia in men (53 patients) with prostate cancer. After adjustment for age and BMI, men with prostate cancer who received ADT for at least 12 months prior to the study had significantly higher fasting glucose as compared with men with nonmetastatic prostate cancer not receiving ADT (p = .01) and age-matched controls (p < .01). Of note, men in the ADT group had a higher BMI compared with the other groups. (overall p = .005). It is thought that long-term male hypogonadism is associated with a decrease in lean body mass and an increase in fat mass, resulting in elevated levels of adiponectins, which in turn, are responsible for causing insulin resistance.61

Alibhai et al performed a cohort study on men age 66 or older with prostate cancer identified through the Ontario Cancer Registry. Men given ADT for at least 6 months or who underwent bilateral orchiectomy were matched with men with prostate cancer who have never received ADT. They reported a higher incidence of DM in ADT use (7.1%, 1,392 patients) versus nonusers (6.0%, 1,181 patients). The adjusted HR was 1.26 (95% CI, 1.16–1.36; p < .0001).62

CONCLUSION

Cancer treatment–induced bone loss and metabolic alterations are an unintentional consequence of therapy. Als and ADT have shown to cause substantial BMD loss. Single-agent chemotherapies, specifically cyclophosphamide, and combination chemotherapy regimens increase the risk of hypogonadism in both genders. Long-term glucocorticoid use is a known risk factor for BMD loss in the noncancer population, but it remains unclear if short-term glucocorticoid use significantly contributes to bone loss in patients with cancer. It is important to screen patients to identify metabolic alterations, because body mass index classifications of overweight and obesity accounted for about 40% of all cancers diagnosed in the United States in 2014.63 Studies have reported that having diabetes was associated with an increased cancer risk.
Integrative Approaches to Reduce Endocrine Therapy–Associated Toxicities

Endocrine therapy is one of the most important adjuvant treatments to reduce risk of recurrence in endocrine-responsive cancers. The two most common adjuvant endocrine therapy–associated toxicities are joint/muscle pain and vasomotor symptoms. Integrative therapies involve the use of nonpharmacologic approaches, such as acupuncture, massage, yoga, exercise, and/or herbal supplements, to alleviate cancer symptoms or treatment-induced side effects. Here, we summarize the latest evidence supporting the use of certain integrative approaches to help alleviate these endocrine therapy–associated toxicities and how to integrate them into oncology practice.

AI-Induced Musculoskeletal Symptoms

AIs are the recommended first-line adjuvant endocrine therapy for postmenopausal women with hormone receptor–positive breast cancer either as monotherapy or in sequence with tamoxifen. Aromatase inhibitor–induced musculoskeletal symptoms (AIMSS) are reported in up to 50% of women, leading to drug discontinuation in approximately 13% of users. The recommended duration of treatment of breast cancer survivors is 5 to 10 years.

There have been four small sample–sized, randomized, controlled trials (RCTs) comparing the effects of real and sham acupuncture in reducing AIMSS, with no substantial adverse reactions to either treatment. Although one of the trials indicates that real acupuncture may be significantly better for joint/muscle pain than sham acupuncture, this finding was not confirmed by the other three trials. The study by Mao et al is the only study among these with an added waitlist control arm, and it shows greater pain reductions with real acupuncture compared with waitlist control but not sham acupuncture. A recently completed three-arm Southwest Oncology Group study (226 patients) showed that 6 weeks of twice weekly real acupuncture followed by another 6 weeks of once weekly treatments was significantly better than sham acupuncture (placebo control) and usual care in reducing AIMSS at both weeks 6 and 12. Remarkably, it also showed longer-term benefits that lasted to the 24-week follow-up, a full 12 weeks post-treatment. Minimal toxicities were associated with the intervention, with 47% of patients experiencing grade 1 bruising.

Given these results from a randomized phase III trial, it is reasonable to suggest that patients with breast cancer try acupuncture for AIMSS. Acupuncture is offered in 90% of oncology centers in the United States, and it is covered by some health insurances. A typical acupuncture session costs between $70 and $150 and takes about 45 minutes. Additional research in this area could focus on cost-effectiveness analysis and implementation.

In addition, exercise may help reduce AIMSS compared with usual care. In a 2015 study, 121 physically inactive patients on AIs with scores of at least three on a 10-point scale for worst joint pain were randomized to 150 minutes of aerobic exercise weekly and supervised twice weekly strength training or usual care for 12 months. Women randomized to the exercise arm had substantial reductions in joint pain, whereas those who received usual care all had increased pain. Given the benefits of exercise for cancer survivors in multiple areas, including metabolism, cardiovascular health, bone health, and cancer prevention, as well as minimal side effects, it is also reasonable to recommend exercise to patients experiencing AIMSS.

Yoga is a traditional Indian practice that incorporates breathing exercises (pranayama) and movement through or by holding postures (asanas). A study exploring the effect of yoga on AIMSS showed that a twice weekly yoga program for 8 weeks improved patients’ balance and flexibility and reduced pain without side effects. A secondary analysis of a multisite RCT also suggests benefits of yoga to improve AIMSS by reducing pain and physical discomfort.

There is preliminary evidence that AIMSS may be related to low serum vitamin D. A double-blind RCT in 60 breast cancer survivors with AIMSS who also had low serum vitamin D levels (less than 30 ng/mL) showed that high-dose supplementation significantly improved AIMSS pain and BMD compared with placebo control. The beneficial effect was stronger in the stratum with lower vitamin D levels (10–19 vs. 20–29 ng/mL).

Lastly, a 2015 RCT comparing omega-3 fatty acids with placebo (soybean/corn oil) in 262 breast cancer survivors with moderate to severe AIMSS showed that both omega-3 fatty acids and placebo resulted in more than 50% sustained reductions in AIMSS but with no substantial between-group differences, raising the question of whether the placebo was truly inert.

Taken together, our recommendations as integrative oncology physicians in the clinic for patients suffering from AI-induced joint/muscle pain are to consider exercise, acupuncture, and yoga for symptom management. Patients’ 25-hydroxyvitamin D levels should be monitored and supplemented with weekly high-dose vitamin D2 if the level is less than 30 ng/mL. Dietary supplements, such as omega-3 fatty acids, could be tried, but they may most likely work via placebo effect.

Vasomotor Symptoms

Vasomotor symptoms, such as hot flashes and night sweats, commonly result from endocrine therapy. Symptom management is challenging, because the most effective treatment, estrogen therapy, is associated with increased risk of recurrence and development of new breast cancers.

Several integrative approaches have been evaluated to alleviate endocrine treatment–related vasomotor symptoms, especially hot flashes. Among these approaches, acupuncture has been studied more extensively, with multiple RCTs completed. Results from a systematic review of acupuncture to control hot flashes in patients with cancer showed significant improvements from baseline in all eight studies evaluated, and they showed that real acupuncture was significantly better than sham for different aspects of hot flashes in three studies.
In addition, a 2016 pragmatic RCT (190 patients) that compared individualized acupuncture plus an enhanced self-care regimen with enhanced self-care alone showed that the combination therapy was superior in reducing hot flush scores at the end of treatment as well as at 3- and 6-month follow-up visits. This study provides solid evidence to support the use of acupuncture to reduce hot flashes and improve quality of life in breast cancer survivors. However, there are no large RCTs comparing real acupuncture with placebo, raising concerns that acupuncture only works via the placebo effect to alleviate vasomotor symptoms. As a result, the Society of Integrative Oncology and the ASCO guidelines still only provide moderate support for the use of acupuncture to treat hot flashes in breast cancer survivors.

In a case series of seven patients with prostate cancer who experienced hot flashes associated with ADT, acupuncture reduced hot flush severity and frequency. In another series of 14 patients with prostate cancer, acupuncture treatment also reduced hot flashes at weeks 2 and 6 as well as 8 months follow-up. In addition, several studies of patients with prostate cancer and hot flashes suggest improvements with various types of acupuncture, warranting additional study of this population.

The current evidence is insufficient for other integrative therapy approaches to alleviate endocrine therapy–related hot flashes, including yoga, meditation, hypnosis, homeopathy, or supplementation with soy, black cohosh, flaxseed, peppermint, or vitamin E. Collectively, these findings guide our recommendations as integrative oncology physicians in the clinic to recommend acupuncture to patients suffering from vasomotor symptoms.

In summary, nonpharmacologic approaches to consider with patients in addressing endocrine therapy–related musculoskeletal symptoms should include acupuncture, exercise, and yoga, and when addressing hot flashes, nonpharmacologic approaches to consider should include acupuncture. Evidence for supplements is lacking, although monitoring for adequate serum vitamin D levels and encouraging a diet rich in omega-3 fatty acids may help improve AIMSS.

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PEDIATRIC ONCOLOGY
Immunotherapy for pediatric malignancies holds the promises of improving outcomes and reducing treatment-related complications. Among different forms of immunotherapy that are actively being pursued, the adoptive transfer of T cells that express chimeric antigen receptors (CARs) has garnered great excitement because of the success of CAR T-cell therapy for CD19-positive malignancies.1-11 CARs are synthetic molecules that combine the specificity of monoclonal antibodies with the effector function of T cells.12-14 The prototypic CAR consists of an antigen binding domain encoded by a single-chain variable fragment derived from a monoclonal antibody, a hinge and transmembrane domain, and signaling domains derived from the CD3.ζ chain as well as costimulatory molecules, such as CD28 and/or 41BB (Fig. 1A). The majority of CAR T-cell products are generated by viral transduction that uses replication incompetent retroviral or lentiviral vectors (Fig. 1B).

Since the submission of the first investigational new drug application for CD19–CAR T cells, the field has moved rapidly and culminated in 2017 with approval by the U.S. Food and Drug Administration (FDA) of two CD19–CAR T-cell products.15 The interested reader is referred to recent reviews, which summarize the clinical results of CD19–CAR T cells in detail.1-2 Here, we highlight only the key findings, which must be considered as we develop and improve current CAR T-cell therapy approaches for pediatric solid tumors.

First, lymphodepleting chemotherapy with cyclophosphamide and fludarabine is critical to allow engraftment and expansion of adoptively transferred CD19–CAR T cells. Second, CD19–CAR T cells can eradicate B-cell malignancies regardless of their underlying genetic alteration. Third, CD19–CAR T cells, can eradicate B-cell malignancies, which are refractory to chemotherapy and/or radiation, highlighting that T cells kill their target cells through different cytotoxic mechanisms than conventional therapies. Fourth, CD19-CARs have to encode a costimulatory signaling domain to be effective. Although CD19–CAR.CD28.ζ and CD19–CAR.41BB.ζ T cells have not been compared directly in a single clinical study, results of published studies indicate that CD19–CAR.41BB.ζ T cells persist longer.1-11 However, it remains unclear whether this translates into improved antitumor activity.1-11 Fifth, targeting a single antigen can result in antigen loss variants. Last, CD19–CAR T-cell therapy can be associated with important clinical adverse effects, including cytokine release syndrome (CRS) and neurotoxicity.1-11

In this educational review, results of early-phase clinical studies with CAR T cells for pediatric solid tumors and brain tumors are summarized (Table 1). In addition, strategies to improve their antitumor activity and current challenges are discussed.
the first study, patients received up to $10^9/m^2$ CD8 CD171-specific CAR T-cell clones.\(^{16}\) Adoptive transfer of T cells was well tolerated, but T cells persisted for only 6 weeks, and only one of six patients had a partial response. One strategy to improve the persistence of adoptively transferred T cells takes advantage of the specificity of the endogenous αβ T-cell receptor expressed by CAR T cells. For example, virus-specific T cells receive appropriate stimulation by viral antigens presented by professional antigen-presenting cells. This concept was explored in the second clinical study, in which investigators expressed a first-generation disialoganglioside (GD2)-specific CAR in polyclonal Epstein Barr virus (EBV)—specific T cells. The in vivo fate of GD2–CAR EBV-specific T cells was directly compared with activated T cells that expressed the same CAR in individual patients.\(^{17,18}\) Although GD2–CAR EBV-specific T cells did not expand, they persisted longer than GD2–CAR activated T cells. Five of 11 patients with active disease showed tumor responses or necrosis. Three of them had complete responses.

More recently, activated T cells that expressed a third-generation GD2–CAR with a CD28.OX40.ζ endodomain were evaluated in patients with neuroblastoma.\(^ {19}\) Three cohorts of patients were infused. The first cohort (four patients) received only CAR T cells; the second cohort (four patients) received lymphodepleting chemotherapy (cyclophosphamide and fludarabine) before CAR T-cell infusion; and the third cohort (three patients) received two doses of pembrolizumab in addition to CAR T-cell infusion: on day −1 and day 21 relative to CAR T-cell infusion. Lymphodepleting chemotherapy induced expansion of CAR T cells for up to 3 logs, and expansion peaked at 1 to 2 weeks post infusion. Addition of pembrolizumab did not improve T-cell expansion or persistence further. There was a large increase in the frequency of circulating myeloid cells in the peripheral blood with an immunosuppressive M2 phenotype after CAR T-cell infusion in all three cohorts. Additional studies are needed to investigate the significance of this finding.

In addition to these published studies, several clinical trials, including one study to evaluate second-generation (41BB.ζ) and third-generation (CD28.41BB.ζ) CAR T cells that target CD171\(^ {24}\) in patients with neuroblastoma and ganglioneuroblastoma (NCT02311621), are in progress. In addition, studies continue to explore GD2–CAR T cells for neuroblastoma; these include NCT02107963, NCT02761915, and NCT03373097.

**Sarcoma**

T cells that express second-generation HER2–CARs (CD28.ζ) have been evaluated in 19 patients with refractory HER2-positive sarcoma (16 with osteosarcoma, one with Ewing sarcoma, one with primitive neuroectodermal tumor, and one with desmoplastic small round cell tumor). HER2–CAR T-cell infusions were well tolerated and had no dose-limiting toxicity.\(^{20}\) HER2–CAR T cells persisted for at least 6 weeks in patients who received greater than $1 \times 10^9/m^2$ HER2–CAR T cells and were detected at tumor sites. Of 17 evaluable

**PRACTICAL APPLICATIONS**

- CAR T cells for pediatric solid tumors are safe but have limited antitumor activity in early-phase clinical studies.
- Carefully designed correlational studies will be critical to understand current failures of CAR T-cell therapies and to devise strategies to improve them.
- Routine, noninvasive, clinical imaging of infused CAR T cells would provide invaluable insight into their biodistribution in humans.
- Additional genetic modifications have improved the antitumor activity of CAR T cells in preclinical models, but improved CAR T cells have not been tested in the clinic.
- Costs and regulatory requirements associated with clinical testing of CAR T cells have the potential to impede progress.
patients, four had stable disease. Three of these had their tumor removed; one showed 90% or greater necrosis. Subsequently, six patients received lymphodepleting chemotherapy before HER2–CAR T-cell infusion. HER2-CAR T-cell expansion was observed without apparent toxicity, and one patient with refractory rhabdomyosarcoma, who had persistent bone marrow disease only, achieved a complete response for greater than 12 months. In addition to HER2–CAR T cells, GD2–CAR T cells are actively being explored (NCT01953900, NCT02107963) for sarcoma. In one study, a third-generation GD2–CAR with a CD28.OX40.ζ endodomain is expressed in varicella zoster virus–specific T cells, and the investigators are evaluating whether GD2–CAR virus-specific T cells can be boosted with an FDA-approved varicella zoster virus vaccine after infusion. Another clinical study (NCT02932956) is approved by the FDA to evaluate the safety and efficacy of GPC3-CAR T cells in patients with pediatric solid tumors, including rhabdomyosarcoma. However, the study currently is not open for accrual.

**Brain Tumors**

Clinical studies with CAR T cells that target HER2, EGFRvIII, and interleukin (IL)-13 receptor α2 (IL-13Ra2) have been conducted in patients with high-grade glioma. Two studies infused only adults, whereas 10 of 17 patients in the HER2–CAR T-cell therapy study were children. T cells were given either intravenously (HER2, EGFRvIII) or directly injected into the tumor and/or ventricle (IL-13Ra2). Like the CAR T-cell therapy studies for solid tumors, the majority of patients in the brain tumor studies had progressive disease. However, responses were observed; these included one partial response and one complete response, and several patients had stable disease for a prolonged period of time.

Detailed correlative studies performed after infusion of EGFRvIII–CAR T cells revealed that T cells were able to migrate to glioma sites after intravenous infusion. Target antigen expression was reduced in resected gliomas, which was indicative of an on-target CAR T-cell effect. In addition, gliomas upregulated the expression of immunosuppressive molecules, including indoleamine 2,3 dioxygenase and IL-10, which highlighted the ability of gliomas to counteract infiltrating pro-inflammatory CAR T cells. Currently, only one clinical study (NCT02208362) is actively recruiting patients, including children older than age 12 years, with gliomas. This study is evaluating the safety and efficacy of intracranial injections of IL-13Ra2–CAR.41BB.ζ T cells.

The initial foray into the clinic with CAR T cells has demonstrated their safety for pediatric solid tumors and brain tumors. However, only subsets of patients have benefited from this approach so far. Potential strategies to increase the efficacy of CAR T cells are reviewed in the next section.

**Strategies to Improve CAR T-Cell Therapy for Solid Tumors**

Lack of CAR T-cell efficacy is most likely multifactorial. Major roadblocks include the availability of targeted antigens and their heterogeneous expression, the homing of T cells to tumor cells, and the immunosuppressive tumor microenvironment (Fig. 2).
Expanding the Repertoire of Targetable Antigens

The majority of CARs developed so far recognize cell surface proteins (GD2, HER2, Glypican (GPC)3, and IL-13Rα2), which originally were discovered as targets for monoclonal antibodies. Efforts are underway with gene expression array data and proteomics to identify new targetable cell surface antigens. However, it might be difficult to discover antigens that are not expressed at low levels in normal tissues. Although private neoantigens are present, albeit at low frequency, in pediatric tumors, directly targeting these with CAR T cells is not feasible with current technology that uses viral vectors to generate CAR T cells. In addition to the large regulatory burden and cost, time is a barrier: it takes more than 6 months to generate a clinical-grade viral vector. However, optimization of CAR T cells to efficiently induce immune responses against nontargeted antigen (i.e., antigen spreading) would be one approach to target private neoantigens and could increase the antitumor activity of CAR T cells in a manner similar to that of cancer vaccines.

CAR T cells are being developed to recognize antigen patterns. Examples include designing CARs that recognize two antigens or engineering T cells that express multiple CARs. T cells that express these CARs become fully activated only in the presence of all targeted antigens. Targeting multiple antigens also should offset the risk of selecting antigen loss variants. In addition, so-called inhibitory CARs that block potential off-target CAR responses have been developed. Development of CARs that recognize peptides in the context of major histocompatibility complex class I molecules also might increase the potential repertoire of targetable antigens, because two-thirds of all expressed proteins reside within the cell. This can be achieved with a single-chain variable fragment derived from a T-cell receptor to mimic a monoclonal antibody as a CAR antigen-binding domain. Examples include CARs specific for an HLA-A2–restricted peptide derived from intracellular proteins, such as Wilms tumor 1 protein or proteinase 3.

Inducible expression systems may provide a potential solution to the antigen dilemma. So-called synthetic notch signaling receptors allow the expression of CARs only after a T cell has migrated to tumor sites, which potentially enables the targeting of antigens that are expressed in normal tissues.

Enhancing Migration of CAR T-Cells to Tumor Sites and Within Tumors

Several preclinical studies have highlighted the mismatch between chemokines secreted by solid tumors and chemokine receptors expressed by CAR T cells. Transgenic expression of chemokine receptors has been shown to overcome this roadblock. For example, neuroblastoma secretes high levels of CCL2; however, CAR T cells lack expression of the corresponding chemokine receptor (i.e., CCR2). Transgenic expression of CCR2b on GD2–CAR T cells resulted in enhanced homing and antitumor activity in preclinical neuroblastoma models. Besides migration to tumor sites, limited migration within tumors might contribute to the reduced antitumor activity observed in clinical studies. For example, CAR T cells are limited in their ability to degrade the extracellular matrix, and this limitation results in poor tumor penetration. However, penetration can be improved by expressing heparanase. Another approach consists of directly targeting cancer-associated fibroblasts, the main producer of collagen within tumors, with CAR T cells.

Engineering CAR T Cells to Resist the Immunosuppressive Tumor Environment

Brain and solid tumors create a hostile tumor environment that favors T-cell exhaustion and/or dysfunction induced by immunosuppressive cytokines (e.g., IL-4, IL-10, transforming growth factor β [TGFβ]); expression of inhibitory molecules (e.g., first apoptosis signal receptor [FAS] ligand, PD-L1); the metabolic environment; and/or recruitment of immunosuppressive cells, including myeloid-derived suppressor cells, cancer-associated fibroblasts, and/or regulatory T cells.

Although this section is focused on engineering CAR T cells to improve their antitumor activity in the tumor microenvironment, combination therapies also are attractive approaches. For example, combination of CAR T-cell therapy with checkpoint blockade, oncolytic viruses, chemotherapy, radiation, and/or small molecules is being explored in preclinical studies with encouraging results. Genetic engineering approaches to enhance the antitumor activity of CAR T cells can be divided into two broad categories: transgenic expression of immune stimulatory molecules and silencing negative regulators.

Several preclinical studies have shown that transgenic expression of cytokines (e.g., IL-12, IL-15, IL-18), constitutive cytokine receptors, 41BBL, or CD40L enhance the antitumor activity of CAR T cells. A recent study also demonstrated that transgenic expression of IL-7 in combination with the chemokine CCL19 not only enhances the effector function of CAR T cells but also enables the cells to induce endogenous T-cell responses against the targeted tumor, which is indicative of antigen spreading. Direct blockade of inhibitory cytokines or conversion of their signal into a T-cell stimulatory signal are other approaches that are being pursued. For example, expression

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**FIGURE 2. Roadblocks of CAR T Cells for Solid Tumors**

- **Antigen & Heterogeneity**
- **CART Roadblocks**
- **Tumor environment**
- **Homing**
of a dominant negative TGFβ receptor renders T cells resistant to TGFβ in preclinical as well as in clinical studies. In addition, dominant negative receptors have been developed to provide intrinsic protection from PD-1/PD-L1 checkpoint blockade. Chimeric cytokine or switch receptors not only block an inhibitory signal but also convert it into a T-cell stimulatory signal. Examples include receptors that consist of the ectodomain of the IL-4 receptor and the transmembrane and intracellular signaling domain of the IL-2 or IL-7 receptor. Although siRNA approaches were used initially to silence negative regulators, more recent studies have focused on gene editing technologies, such as TALENs and CRISPR/Cas9. Pertinent examples include the silencing of FAS ligand or the knockout of PD-1 in T cells.

As we enhance the effector function of CAR T cells, it is advisable to insert safety switches that can be activated if adverse effects develop. Safety switches that have been tested clinically include HSV thymidine kinase (HSV-tk), which enables cell killing in the presence of ganciclovir, or an inducible caspase 9, which can be activated by a chemical inducer of dimerization. In addition, expression of cell surface molecules (e.g., EGFR, CD20), which can be targeted with FDA-approved monoclonal antibodies, is another suicide gene option that has been evaluated successfully in preclinical models.

CURRENT CHALLENGES
CAR T-Cell Generation
The majority of clinical studies have used retroviral or lentiviral vectors to generate clinical-grade CAR T-cell products. Generation of clinical-grade viral vectors is time consuming and costly, and their use is associated with a large regulatory burden. In this regard, reducing some of the required testing of CAR T-cell products, as recently advocated, would be a step in the right direction. Required testing could also be reduced with the use of nonviral DNA delivery systems that have been successfully used to generate CAR T cells. Closed-cell manufacturing systems and the use of off-the-shelf CAR T-cell products also hold the promise to streamline CAR T-cell production and/or distribution.

What Is the Optimal T-Cell Subset to Generate CAR T Cells?
Several studies have highlighted that CAR T cells generated from central memory T cells with a defined CD4:CD8 ratio have superior effector function compared with CAR T cells generated from bulk T cells in preclinical models. Epigenetic profiling of T cells has provided novel insight and holds the promise to advance our ability to select the most potent T-cell subset for CAR T-cell generation. Also, γδ T cells and invariant natural killer T cells are being explored as T-cell platforms for CAR T-cell therapy. In this regard, a clinical study with invariant natural killer T cells that express GD2–CARs and IL-15 for patients with neuroblastoma has been approved by the FDA (NCT03294954) but is not actively accruing patients.

Need for Preclinical Testing in Range of Animal Models
The majority of preclinical studies have relied on xenograft models, which do not reliably recapitulate the complex tumor microenvironment. Immunocompetent animal models have been adapted for CAR T-cell therapies, and these models will be invaluable as combination therapies are developed. In addition, patient-derived xenograft models should enable preclinical testing of CAR T cells against a panel of human tumors that more closely mimic patient tumors than tumor cell lines that have been propagated in vitro. Also, large animal models hold promise to evaluate CAR T cells in spontaneous tumor models.

Correlative Studies, In Vivo Tracking of Infused T Cells, and Clinical Response Criteria
There currently is only one published CAR T-cell therapy (noted in the Brain Tumor section) that has systematically studied tumor biopsies after infusion. These types of studies will be critical to understand current therapeutic failures and to devise evidence-based approaches to overcome them. In addition, our ability to track infused CAR T cells in patients is limited unless the cells are genetically modified with a reporter gene, such HSV thymidine kinase. The ability to routinely track CAR T cells for 48 to 72 hours after infusion would be a major advance that could provide invaluable insight into initial biodistribution of CAR T cells and their ability to migrate to tumor sites. Although diagnostic imaging immune response criteria have been implemented for the assessment of immunotherapies for solid tumors and brain tumors, these were developed in the cancer vaccine era and might require additional fine tuning for cell-based immunotherapies, including CAR T cells.

CONCLUSIONS
The initial foray of CAR T cells into the clinic for pediatric solid tumors and brain tumors demonstrated their safety but also highlighted their limited antitumor activity. Additional genetic modification of CAR T cells has greatly enhanced the antitumor activity of these cells in preclinical studies, and we hope that some of the devised strategies will translate into improved antitumor activity in humans. To advance the field, there is an urgent need to discover novel antigens that can be targeted with CAR T cells and to improve our ability to evaluate CAR T-cell therapies in preclinical models. The abilities to track CAR T cells noninvasively and to perform detailed studies with patients enrolled in CAR T-cell therapy should enable us to advance the field. We remain hopeful that, within the next 5 to 10 years, patients with solid tumors will benefit from CAR T-cell therapies to the same degree that patients with B-cell–derived malignancies do today.

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Supporting Caregivers of Patients With Cancer: A Summary of Technology-Mediated Interventions and Future Directions

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OVERVIEW

This paper aims to review literature published on the support of cancer caregivers with health technology. Eighteen articles were reviewed to better understand cancer caregiving and categorized into four different themes: (1) design guidelines, (2) information facilitation, (3) social support, and (4) multicomponent interventions. Analysis of the current articles revealed that there are substantial gaps in knowledge regarding a range of health technologies that facilitate family caregiver support and its distribution to health institutions. Further research is needed in this area, as family caregivers are primary providers of essential elements of care to patients. Future studies should unpack existing barriers that interfere with the development of health technology interventions in cancer care.

Approximately 43.5 million caregivers have provided unpaid care to an adult or child in the last 12 months in the United States. Caregiving for patients with cancer has been described as an “intense, episodic, and challenging care experience.” For 2017, an estimated 1,688,780 individuals received a new cancer diagnosis, and cancer death rates have been declining since the early 1990s. Survivorship has steadily improved, and the need for caregivers providing longer duration of care in the outpatient or home setting has also increased. Moreover, the nation is experiencing changing demographics with greater ethnic, racial, social, religious, and geographic diversity. Families are more widely dispersed, and both men and women of the household are in the workforce. More than ever, there is an urgent need to provide innovative solutions that account for these new challenges as well as address caregiving needs throughout the cancer trajectory.

There is broad agreement that caregiving an individual with cancer is challenging and can adversely impact quality of life (QOL), and family caregivers are more likely to experience physical, social, and emotional distress compared with noncaregivers. Particularly in the cancer setting, caregivers are providing multifaceted supportive medical care (i.e., medication administration, symptom management, and transportation), but often are not equipped with the necessary information, skills, and confidence to perform these complex tasks. This is especially problematic when caregivers are feeling overwhelmed. It is not surprising that their own physical and mental health may be negatively impacted, which may adversely affect patient health outcomes. An extensive literature base supports that caregiver interventions have the potential to improve caregiver QOL and emotional well-being for adult patients with cancer and alleviate distress in caregivers of pediatric patients with cancer. Nonetheless, it also highlights the gaps in the field. Further, growing evidence supports the need for multimodal components, such as education and medical skills training, self-care, and coping-skills training. However, the dose and intensity and when along the cancer trajectory this should occur are not well established. Importantly, even when evidence demonstrates the effectiveness of a caregiver intervention, translation into clinical practice remains a major challenge. An urgent need for action to address these issues through research recommendations has recently been made by many researchers, which include: “(1) improving the assessment of the prevalence and burden of informal cancer caregiving; (2) improving interventions targeted at [patients with cancer], caregivers, and patient-caregiver dyads; (3) facilitating further integration of caregivers into formal health care settings; and (4) maximizing a positive impact of technology on informal cancer caregiving.” Indeed, rapid advances in technology provide a unique platform for delivery of flexible and scalable caregiving interventions, particularly with widespread use of electronic medical record (EMR) systems across institutions.

With demographic and social changes, such as the aging population, home-based care is becoming increasingly critical to the health care system. Although some research suggests positive effects resulting to caregivers, being a primary caregiver is commonly perceived as a chronic
stressor due to unfamiliar medical situations and a sense of anxiety that permeates through life on the most daily level.15 Caregivers with little or no medical training are often underprepared, but they are expected to understand, remember, and report the patient’s symptoms appropriately on behalf of their loved one from the moment of the initial diagnosis.16 These burdensome experiences can result in negative physical, emotional, and social effects on their daily lives and even affect their physical well-being.15

To improve care delivery and outcomes, recent studies have discovered possibilities to address family caregiver needs and provided a variety of supportive interventions.9,17,18 Reported interventions support that patients undergo the harrowing process of cancer treatment, and their caregivers must continuously attend to their physical and emotional needs.11

The objective in this review is to provide readers with an overview of cancer-caregiving interventional trials with a focus on novel technology-based solutions for family caregivers. We performed a systematic literature search using PubMed, the Association for Computing Machinery Digital Library, and Cochrane Library. We also include an exemplar from pediatric oncology highlighting Bright IDEAS problem-solving skills training for caregivers in the pediatric cancer setting. From bench to bedside, we examine how this group of pediatric psychosocial providers has used a stepwise approach in studying the acceptability, effectiveness, and current next steps of translating this evidence-based intervention into widespread clinical practice through a process of implementation and dissemination research.

### PRACTICAL APPLICATIONS

- A majority of reviewed interventions are weighted toward information facilitation, such as providing specific medical information to caregivers through educational websites or smartphone applications. Minimal work focused on promoting active participation through two-way communication with providers or peers.
- The studies identified in this review provide valuable lessons for designers and health care practitioners. Notably, the study found various educational/informational interventions that have been developed to assist caregivers and have been widely used by health care institutions.
- Our review indicates that there are a paucity of data related to helping caregivers of patients with cancer, as well as a standardized approach to active dissemination, implementation, and adoption of developed interventions. One example of dissemination and implementation is provided within the pediatric cancer setting: Bright IDEAS.
- Iterative cycles of user-centered approaches with standardized measurement scales and research methods are critical prior to implementation in the clinical environment to improve usability and avoid unintended consequences of technology.

### BACKGROUND

Cancer is the second leading cause of death in the United States.12 In most cases, cancer treatment requires long-term medical care and support. Many patients with cancer rely on family and friends to assist with cancer treatment needs, and their family members often take the primary responsibility as the caregiver.11 Family caregivers are defined as individuals (for example, a parent, spouse, family member, friend, or neighbor) who provide care that is typically unpaid for, usually takes place at home, and involves considerable amounts of time and energy.2 Due to the harrowing nature of the illness, being a caregiver for a family member with cancer requires multifaceted activities that are physically, emotionally, socially, and financially demanding.19,20

Caregiving tasks include monitoring symptoms, dealing with various side effects, tracking medical information; and providing emotional and clinical support.16,21 Daily routines are also negatively affected, and many caregivers become isolated from their family and friends.72,23 In addition, the caregiver’s performance influences the coping style of the patient with cancer, such as managing depression that can originate from the ordeal of living with cancer.7,24 Unfortunately, negative emotions (i.e., anxiety, depression, and symptoms of posttraumatic stress) can be stressful for patients and ultimately impact both patients’ and caregivers’ health.25 Despite the significance of their role, the manifold needs of caregivers are easily overlooked by the health care system; there are inadequate data showing approaches that are effective at easing caregiving burden. It has been described that better-supported caregivers feel a sense of improved self-efficacy and well-being, a change that also causes a positive impact on the health outcomes of patients themselves.15,25 Cancer caregiving could be optimized through interventions targeted at enhancing medical information delivery, teaching coping skills, social relationships with their family or friends, and self-care practices.26

As EMR systems have been actively adopted within care institutions, health technology is becoming increasingly commonplace in the clinical environment. With health technology, patients and caregivers can readily receive health information, including laboratory results or changes on medications, and report specific symptoms to health care practitioners remotely from home.27 In recognition of the unique and critical role that caregivers play in the chronic care context, multiple technological interventions have been designed to assist caregiving tasks.28,29 For example, in caregiving research, a research program called Resources for Enhancing Alzheimer’s Caregiver Health investigated the efficacy of caregiving support interventions in reducing depressive symptoms among of caregivers of patients with Alzheimer disease.30 The study showed that caregivers in the combined family therapy and computerized telephone system experienced a substantial reduction of depression.

Research evaluating these interventions has shown that e-health technology can empower caregivers by providing them with a platform of useful resources. Recent research in the cancer treatment context has shown that most caregivers...
of patients with cancer readily use advanced technology, and over two-thirds of caregivers want mobile technology that supports their caregiving efforts. In addition to such pervasiveness of health technology among cancer caregivers, it has also been shown that cancer caregivers actively use social media such as Facebook or YouTube to share their cancer-related experiences, acquire information, and seek social support. Although evidence has shown that health technology interventions have the potential to alleviate current caregiving constraints for caregivers, only a limited amount of literature exists that probes the influence of mobile health technology on caregivers.

Previously published reviews investigating intervention targets for caregivers have broadly focused on the use of multimedia for caregiver education, the role of the internet in caregiving, measurement of caregiver well-being and distress, shared decision-making, basic caregiver needs, and help with pain management. Most of these reviews have also focused on the nontechnological interventions, such as education programs or information delivery. To our knowledge, no such review has been conducted on the impact of technology-aided interventions on family caregiving. This deficiency generates a considerable gap in the cancer caregiving literature, particularly as a new stream of supporting technological interventions is successfully alleviating the caregiving burden.

This paper reviews the field of supportive health technology interventions for caregivers and subsequently analyze and synthesizes the resulting insights to discover further possibilities of caregiver engagement and assistance. Investigating effective technology interventions could alleviate caregiver burden, improve patient outcomes, and potentially be applied for use in many other caregiver populations.

METHODS

This study adopted Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Fig. 1).

Three literature databases were searched: PubMed, Association for Computing Machinery Digital Library, and the Cochrane Database of Systematic Reviews. The initial searches included terminology that was used to identify research that (1) aimed to improve caregiving (“family caregiver,” “caregiver,” “support caregiver,” or “caregiver engagement”), (2) was associated with health technology (“technology,” “intervention,” “e-health,” or “m-health”), and (3) was conducted in the cancer context (“cancer,” “cancer caregiving,”...
or “cancer patient”). The detailed searches for the different databases are available upon request. For example, PubMed offers exact search functions to narrow down by specific diseases. The initial database search was limited to articles published in the English language, research involving human subjects, and publications from 2008 to 2017. Because of rapid technological changes, we limited our search to studies published within the last 10 years. Title and abstract of articles from the search were reviewed by two researchers and chosen based on inclusion criteria. Additional articles were added by reviewing references of the searched articles from three databases. Articles selected for full review were followed by in-depth analysis to categorize into four themes: information delivery, communication facilitation, social support, and design guidelines. Some of the studies were identified holistically accommodating all of four themes. We summarize the findings (Table 1).

RESULTS
A total of 1112 results was found: 747 from PubMed, 353 from the Association for Computing Machinery Digital Library, 7 from Cochrane, and 5 articles were added by reviewing references of the searched articles from three databases. Of the 1112 results found, 64 qualified for full review. Studies were excluded if they mainly targeted other caregiving populations (e.g., other disease populations) or if there were no technology intervention/guidelines described. We also included conference proceedings and journal papers, but protocols, abstracts, or review papers were excluded. Of those that are eligible for full review, 18 were included in the final results. Three were randomized controlled trials (RCTs), and others followed quasi-experimental or qualitative interviews and observations from the 18 included studies. Of the results, the following studies were classified as: three design guidelines, eight information facilitation, three social support interventions, and four that were multicomponent interventions.

Design Guidelines
Because there are barriers to implementing health technology in health care institutions, such as medical information security, cost, and technology literacy, researchers have strived to understand major needs and challenges.

Kaziunas et al42 conducted field observations and interviews of pediatric patients receiving hematopoietic stem cell transplantation (HSCT) and caregivers to identify informational challenges in an inpatient setting. The study outcomes suggest that participants hoped to navigate the health system, learn to communicate effectively with their care team, and manage the daily challenges of caregiving. Unprepared transitions from inpatient care to long-term outpatient follow-up were also identified as a major challenge.

A study by Gage-Bouchard et al33 examined how caregivers use personal Facebook pages for health-related communication. Analysis of 12 months of data showed that Facebook pages offer a platform for caregivers to share their experiences, promote advocacy and awareness, and optimize social support. As Facebook functions as a tool for communication, information, and support, researchers argue that providers must recognize the importance of social media as a vehicle for support and communication with family caregivers of patients with cancer. Although some studies focus on general hospitalized patients, rather than a specific population, researchers have conducted studies to define patients’ and caregivers’ needs during hospitalization.

Miller et al43 identified key design considerations for technology to support caregivers during hospitalization. Researchers conducted an interview and observation study of patients and caregivers to understand participants’ collaboration in managing their illness. The study demonstrated how patients and caregivers define their roles and responsibilities throughout a hospital stay. As a result, five different roles of caregivers emerged: companion, assistant, representative, navigator, and planner.

Information Facilitation
The majority of included studies examined caregivers’ information needs to enhance their experiences. Health literacy is especially critical for caregivers due to the complexity of the procedure, the amount of information they confront over the course of the illness pertaining to treatment options and medications, and the feasibility of death. Because low health literacy is shown to associate with low adherence to medications, poor health status, and increased treatment costs,59 many researchers have focused on providing medical information and facilitating communication between caregivers and medical providers at the right times.

For example, Song et al44 conducted a pilot study to examine feasibility and acceptability of Prostate Cancer Education and Resources for Couples, a web-based, couple-targeted intervention. Recruitment rates, pre- and postpilot assessments, and website activities (e.g., number of logins and time spent on the site) were evaluated quantitatively. Postpilot interviews were conducted as qualitative evaluations. Both qualitative and quantitative analyses suggested that Prostate Cancer Education and Resources for Couples is useful for patients with prostate cancer and their spouses, notably improving their knowledge about medical symptoms and how to manage them. Findings suggested that the intervention is particularly useful for those who live in rural areas where access to medical care is more challenging.

Slater et al35 also developed and evaluated the Oncology Family App with the aim of providing easy access to useful resources, such as management plans for the illness and individualized health information. The collaborative team consisted of caregivers and clinicians who worked on the development of the app and then refinement of the app following interviews with family groups. Participants’ opinions were favorable regarding the app, and the result suggested that the Oncology Family App was an efficient and convenient way to provide necessary medical information.

Similarly, a prototype website called CARES was designed by Badr et al44 to provide information, coping strategies, and
### TABLE 1. Summary of Findings in the Literature

<table>
<thead>
<tr>
<th>First Author and Reference</th>
<th>Aims</th>
<th>Number of Participants</th>
<th>Measured Factors/Variables</th>
<th>Outcomes</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaziunas et al42</td>
<td>To identify informational challenges of HSCT caregivers and patients in the inpatient hospital setting</td>
<td>17</td>
<td>Patients’ and caregivers’ experience with HSCT, emotional challenges of HSCT, and information that the caregiver needed about the HSCT process</td>
<td>Recommendations to meet the informational needs: (1) provide real-time access to EHR data, (2) provide information about the clinical trials in which the patient is enrolled, (3) provide information about the patient’s care team, and (4) proper preparedness before/at discharge.</td>
<td>Design guidelines</td>
</tr>
<tr>
<td>Gage-Bouchard et al33</td>
<td>To expand upon previous research by examining how cancer caregivers use personal Facebook pages for cancer-related communication</td>
<td>N/A</td>
<td>Themes in cancer-related exchanges from 18 publically available Facebook pages hosted by parents of children with acute lymphoblastic leukemia</td>
<td>Six themes emerged: (1) documenting the cancer journey, (2) sharing emotional strain associated with caregiving, (3) promoting awareness and advocacy about pediatric cancer, (4) fundraising, (5) mobilizing support, and (6) expressing gratitude for support.</td>
<td>Design guidelines</td>
</tr>
<tr>
<td>Miller et al43</td>
<td>To identify key design considerations for technology to support patients and caregivers during a hospital stay</td>
<td>48</td>
<td>Patients’ and caregivers’ experiences in receiving and communicating information during the hospitalization/communication themes</td>
<td>Suggestions in key design considerations based on five defined caregiving roles: companion, assistant, representative, navigator, and planner.</td>
<td>Design guidelines</td>
</tr>
<tr>
<td>Song et al44</td>
<td>To evaluate the feasibility and acceptability of prostate cancer education and resources for couples</td>
<td>26 dyads</td>
<td>General and prostate cancer-specific symptoms, QOL, psychosocial factors, the intervention’s ease of use, and web activities</td>
<td>Improvement in overall QOL and physical and social domains of QOL for patients. Web activity data indicated high PERC use.</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Slater et al45</td>
<td>To develop and evaluate the mobile app for cancer family caregivers</td>
<td>15</td>
<td>Development of a design intervention/features and functionality of the app</td>
<td>Frequent use in Blood Results Table, When to Call, and Statewide Hospital Contacts modules.</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Badr et al46</td>
<td>To develop and evaluate a dyadic, web-based intervention to improve survivor self-management and survivor/caregiver needs and potential design features: attractiveness, controllability, efficiency, intuitiveness, and learnability of the intervention</td>
<td>25 (phase I) and 11 (phase II)</td>
<td>Needs and potential design features: attractiveness, controllability, efficiency, intuitiveness, and learnability of the intervention</td>
<td>High scores in dimensions of attractiveness, controllability, efficiency, intuitiveness, and learnability (received a total usability score of 80 out of 100).</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Collinge et al47</td>
<td>To evaluate the outcomes of a multimedia instructional program</td>
<td>97 dyads</td>
<td>Symptom severity, QOL, perceived stress, and caregiver attitudes</td>
<td>Considerable reductions in all symptoms occurred for patients after both activities: reading vs. massage.</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Walsh et al48</td>
<td>To engage stakeholders in the development of a home medication support intervention and evaluate the acceptability and usefulness of the intervention</td>
<td>16</td>
<td>Development of a design intervention/medication error rates</td>
<td>High acceptability of the intervention; no substantial change in error rates</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Modi et al49</td>
<td>To assess barriers to clinic attendance and the feasibility of a web-based assessment tool to promote problem solving on clinic appointments.</td>
<td>30 dyads</td>
<td>Module’s user-friendliness, format, and potential for use in clinic</td>
<td>High degree of usefulness and preference of the program were received.</td>
<td>Information facilitation</td>
</tr>
</tbody>
</table>

Continued
<table>
<thead>
<tr>
<th>First Author and Reference</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Hong et al50</td>
<td>To investigate experiences of caregivers and patients with the PHR</td>
<td>23 dyads</td>
<td>Usage and experiences with the PHR</td>
<td>Favorable assessments from both caregivers and patients; different usages among caregivers reported</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Dalal et al51</td>
<td>To evaluate the enrollment strategy, use, and usability of patient tools and the content of patient-generated messages</td>
<td>239</td>
<td>The number of enrollees, the total number of times each patient visited the portal page, the total number of messages sent to the care team per individual patient, the number of messages viewed by notified, and the number of provider responses/usability and satisfaction</td>
<td>Favorable evaluation in the average system usability and satisfaction</td>
<td>Information facilitation</td>
</tr>
<tr>
<td>Haldar et al52</td>
<td>To explore the opportunities for a hospital-based peer support system</td>
<td>146 (phase 1) 15 (phase 2)</td>
<td>Patients’ and caregivers’ experiences with an undesirable event/types of advice hospitalized individuals were compelled to share with their peers</td>
<td>Recommendations on three design considerations: (1) leveraging the EMR to match peers, (2) protecting privacy and anonymity, and (3) accommodating dynamic interactions and needs.</td>
<td>Social support</td>
</tr>
<tr>
<td>Northouse et al53</td>
<td>To examine the feasibility of translating an efficacious nurse-delivered program</td>
<td>38 dyads</td>
<td>Emotional distress, QOL, benefits of illness/caregiving, communication, support, and self-efficacy</td>
<td>Marked decrease in emotional distress, increase in QOL, self-efficacy, and perceived benefits of caregiving; notable improvement in self-efficacy; no changes in communication.</td>
<td>Social support</td>
</tr>
<tr>
<td>Fuentes et al54</td>
<td>To explore how persuasive mobile technologies promote the self-reflection and introspection of communication practices, emotions, and lifestyle</td>
<td>6 (phase I) and 6 (phase II)</td>
<td>Social isolation, emotions, and lifestyle of caregivers/feasibility and usefulness of the intervention</td>
<td>Useful feedback on the interventions (nurture social relationships, positive impact in social isolation) and favorable assessment with visualizations</td>
<td>Social support</td>
</tr>
<tr>
<td>DuBenske et al55</td>
<td>To report the impact on caregiver burden, disruptiveness, and mood of providing caregivers access to the intervention vs. the internet with a list of recommended lung cancer websites.</td>
<td>285</td>
<td>Caregivers’ disruptiveness, burden, and negative mood</td>
<td>Caregivers in the CHESS reported lower burden and negative mood than those in the internet group; no significance in the effect on disruptiveness</td>
<td>Multicomponent intervention</td>
</tr>
<tr>
<td>Chih et al56</td>
<td>To assess the effects of an online symptom-reporting system on caregiver preparedness, physical burden, and negative mood</td>
<td>235 dyads</td>
<td>Caregiver preparedness, physical burden, and negative mood</td>
<td>Caregivers’ CHESS + CR group reported less negative mood than those in the CHESS-Only group; no noteworthy difference in caregiver preparedness or physical burden</td>
<td>Multicomponent intervention</td>
</tr>
<tr>
<td>Mayer et al57</td>
<td>To describe the process used to create a pediatric transplant-specific web-based education and support module</td>
<td>23 (phase I), 161 (phase II), and 16 (phase III)</td>
<td>Unmet needs of users and potential functionality of the interventions</td>
<td>Development in HSCT-CHESS website/favorable feedback on initial pilot usability test</td>
<td>Multicomponent intervention</td>
</tr>
<tr>
<td>Runaas et al58</td>
<td>To assess the impact of the tablet-based intervention.</td>
<td>10</td>
<td>Recurring themes regarding caregivers’ uses of the intervention</td>
<td>Caregivers found the tool useful and easy to use, leading them to want even greater access to information.</td>
<td>Multicomponent intervention</td>
</tr>
</tbody>
</table>

Abbreviations: CR, clinician report; EHR, electronic health record; HSCT, hematopoietic stem cell transplantation; N/A, not applicable; PERC, Prostate Cancer Education and Resources for Couples; QOL, quality of life.
support services for survivors of oral cancer and their caregivers. Semistructured interviews with patients and caregivers were conducted to capture information and support needs as well as preferences on website features. Usability assessments uncovered issues related to intuitiveness, navigation, and design of the website. The website was evaluated favorably on the dimensions of attractiveness, controllability, efficiency, intuitiveness, and learnability. Another example is an RCT by Collinge et al\(^\text{47}\) conducted to evaluate a multimedia instructional program for family caregivers with the aim of providing comfort to patients with cancer through simple touch-based techniques at home. Participants were randomized to experimental (multimedia instruction in touch and massage methods) or attention control (reading instruction) groups. Patients with cancer and their caregivers were asked to report changes in symptom severity, QOL, perceived stress, and attitudes. The result shows that multimedia instruction in touch methods offered family members enhanced self-efficacy and satisfaction in caregiving, as well as decreased patient pain, depression, and related symptoms. When using the intervention, family members were trained to apply strategies that enhance patients’ positive moods and reduce distress.

In addition to providing information and education, other researchers focused on meeting specific medical needs, such as medication management and adherence to clinic appointments. Walsh et al\(^\text{48}\) developed a web-based intervention (Home Medication Support) to provide multipurpose functions related to medication management. Home Medication Support includes a medication calendar, a communication tool, side-effect information, and a conversion chart. A usability test was conducted in the second phase of the project with medical record reviews, telephone interviews, and a survey to access usefulness of the intervention and medication error rates.

A recent pilot study conducted by Modi et al\(^\text{49}\) examined the potential of using web-based technology to provide a standardized assessment of adherence to clinic appointments for patients with sickle cell disease. Although both studies required more large-scaled assessments to prove a positive impact of interventions, they introduced novel approaches to supporting caregivers.

Hong et al\(^\text{50}\) conducted a mixed-methods study with adolescent patients and their family caregivers to understand experiences of a personal health record (PHR) system. Through analyses of usage logs, surveys, and interviews, researchers found that both caregivers and patients valued the PHR system; the study recognized different usages among caregivers (for example, caregivers made more use of messaging features). Patients generally had more confidence in managing their health when using the PHR system.

Dalal et al\(^\text{51}\) implemented a web-based, patient/caregiver-centered toolkit that engages patients/caregivers with the plan of facilitating education and patient-provider communication in oncology units and medical intensive care. Usage of patient tools was measured using a System Usability and Satisfaction Survey with patients and caregivers. As a result, the use of educational content was highest for medications and test results and lowest for problems. The most common clinical theme identified was health concerns, needs, preferences, or questions.

**Social Support**

In addition to improving information delivery and communication, there are efforts to assist caregivers using social support. Because offering care to patients with cancer is commonly perceived as a chronic stressor, several studies have investigated interventions, including peer connections and psychoeducational assistance, to provide social support. Research outcomes found that interventions resulted in reducing negative physical, emotional, and social effects on caregivers’ daily lives.

Dalal et al\(^\text{51}\) explored opportunities for hospitalized individuals to have a peer support system, such as online health communities, support groups, and mentoring systems. Surveys and semistructured interviews were conducted, and five benefits of peer support were identified: medication details, information on providers, report and avoid medical errors, emotional support, and time management in the hospital.

Northouse et al\(^\text{52}\) tested the feasibility of translating an intervention, called FOCUS Program, for patients with cancer and their family caregivers into a tailored, web-based format. FOCUS Program contained five modules that spelled the acronym FOCUS: family involvement, optimistic outlook, coping effectiveness, uncertainty reduction, and symptom management. Measured outcomes included emotional distress, QOL, and benefit of illness or caregiving. A pre- and postintervention feasibility study was done to understand the feasibility of using a web-based format to deliver the FOCUS Program. The results suggested that it is possible to translate a clinician-delivered program to a web-based format that was easy to use and had positive effects on dyadic outcomes.

To engage users, other researchers actively used visual components of health technology. Fuentes et al\(^\text{53}\) designed a mobile system called EmotionMingle, showing an image tree that maps a caregiver’s social network with the goal of mitigating social isolation. The mobile system also provides information to caregivers as to how their emotions correlate with their daily communication practices. The results of a qualitative assessment of the study indicated that family caregivers perceived it as useful tool and its visualizations as appropriate.

**Multicomponent Interventions**

Although most of the interventions included in this article had the intent of alleviating caregiver burden, a few studies provided a more holistic view encompassing informational, communicational, and social aspects of caregiving with practical design solutions.

A web-based tool known as Comprehensive Health Enhancement Support System (CHESS) that provides cancer-related information, communication, and a coaching system...
has been shown to help alleviate the negative moods of caregivers of patients with lung cancer.\textsuperscript{55} RCTs compared the impact on caregiver burden, disruptiveness, and mood of providing caregivers with access to CHESS versus a list of recommendations for lung cancer websites. DuBenske et al\textsuperscript{55} demonstrated that CHESS had lower burden and negative mood after 6 months than those with access to the websites only.

Chih et al\textsuperscript{56} investigated the effects of an online symptom-reporting system on caregiver preparedness, physical burden, and negative mood. Patients with cancer and their caregivers at five outpatient oncology clinics were randomly assigned to two groups. Caregivers who used the online support system with timely communication with clinicians reported less negative mood than those who used the online support system only. The study found that by using the online support system, caregivers might experience less negative mood due to the communication with clinicians to meet their needs in management of symptoms for patients. The researchers argued that by adopting useful communication technologies, providers could offer timely support to family caregivers in managing cancer symptoms effectively at home.

As an extension of the original successes of CHESS in the context of patients with lung cancer, Mayer et al\textsuperscript{57} developed the HSCT-CHESS for caregivers and patients of pediatric HSCT. The study conducted a needs assessment through focus groups and surveys. Reported findings guided an interdisciplinary team of family caregivers, providers, engineers, and design teams to develop the refined intervention, HSCT-CHESS.

Similarly, in the HSCT context, BMT Roadmap was developed by Runaa et al\textsuperscript{58} to integrate the personal health information of pediatric patients with HSCT and provide several domains: laboratory results, medications, clinical trial details, photos of the health care team, trajectory of transplant process, and discharge checklist. The tool was provided to caregivers of patients undergoing a first-time HSCT. Qualitative interviews to evaluate the impact of the tool were conducted throughout the patient’s hospitalization on a weekly basis, as well as at discharge and day 100. Study participants found the tool helpful and easy to use, leading them to desire more access to information.

**DISCUSSION**

A major goal of this review was to examine published literature on supporting caregivers of patients with cancer using technology-assisted interventions. The results of our review suggest that the use of health technology-based intervention methods in support of caregivers is still in its infancy. We found that only a few interventions were rigorously and systematically tried in the clinical environment. Moreover, to our knowledge, pre- and post-tests about information facilitation were not conducted. As caregivers represent a critical extension of the clinical environment, it would be beneficial to identify tailored technology interventions with standardized measurement scales and research methods that might be useful. To that end, multiple iterations of user-centered approaches are critical prior to implementation in the clinical environment to improve usability and avoid unintended consequences of technology.\textsuperscript{57,60} For example, involving caregivers and patients from the early stage of the intervention development process would lead to an improved, functional product.\textsuperscript{61}

As per our analysis, most existing interventions were weighted toward information facilitation (8 of the 18 studies), such as providing specific medical information to caregivers through educational websites or smartphone applications. In other words, study outcomes focused on providing medical information. Minimal work focused on promoting active participation through two-way communication with providers or peers. However, considering the complexity and specificity of symptoms experienced by patients with cancer, generic health information would not effectively accommodate a large number of patients. The adaptation of EMR systems within health care institutions and the widespread adoption of health technology would enable patients and caregivers to play an active role in their care. To provide valuable communication, it would be critical for the caregivers to gain access to necessary information as well as provide relevant information for clinicians. Future studies should address additional ways to address caregivers’ needs.

Methodological aspects of the existing study would merit an investigation as well. Most of the studies we have introduced in this review included small numbers of participants to conduct semistructured interviews and measured the success of each intervention. We found very few interventions guided by a theoretical framework. Further, only three studies followed a randomized controlled design with large numbers of participants.\textsuperscript{47,55,56} For example, DuBenske et al\textsuperscript{55} reported positive results of improving the caregiver’s mood with RCTS. As most of our reported study conducted pilot feasibility trials, the study result suggested the future possibility of using randomized controlled design to further validate an impact of suggested interventions.

In addition, the success level of individual interventions was evaluated with various measurement methods. Some of the studies used widely used questionnaires, and others used Likert scales that measure the general QOL as a caregiver, including measures of social support or life satisfaction.\textsuperscript{44,53,56} Other studies developed their own instruments or conducted qualitative interviews to gain deeper user insights.\textsuperscript{42,43,50,58} Specifically, Collinge et al\textsuperscript{47} used the Functional Assessment of Cancer Therapy-General and the Perceived Stress Scale to evaluate the perceived stress levels of caregivers and overall adjustment of caregivers. DuBenske et al\textsuperscript{55} reported each intervention’s effect on caregivers’ disruptiveness, burden, and negative mood with Caregiver Quality of Life Index-Cancer and Profile of Mood States scales. In contrast, some studies evaluated the usability of a given intervention through a semistructured interview investigating the caregiver’s experience with the intervention.\textsuperscript{45,46,49,54} Also, another group of researchers adopted semistructured
interviews exploring the caregiver’s experience, emotional challenges, and information that the caregiver needed.\textsuperscript{33,42,43} Reported findings from included studies generally indicate that caregiving technologies could bring about various positive results, including lower stress and negative mood,\textsuperscript{53,55} or improve engagement.\textsuperscript{58} However, there is no unified measurement instrument and standardized observation period to define the relative success of interventions. This lack of consistency prevents researchers from unifying insights from multiple different studies. Unstandardized methodologies often beget biased results and create challenges for researchers who would compare and contrast the results of various studies. Even though some studies were conducted to address similar objectives, comparing the impact of each intervention is almost impossible with current study results.

Despite such shortcomings, the studies identified in this review provide valuable lessons for designers and health care practitioners. Notably, we could find that a majority of nontechnological, educational/informational interventions have been developed to assist caregivers and have been widely used by health care institutions.\textsuperscript{9} Contents or approaches to the developed interventions would be turned into an advanced platform with technologies. In addition, although there are novel design guidelines that take advanced technology into consideration,\textsuperscript{62} multiple obstacles must be overcome before such interventions could be effectively implemented. Interventions like Bright IDEAS\textsuperscript{10,63} supply important insights into potential solutions to such persistent issues.

In pediatric oncology, investigators have completed two large RCTs with Bright IDEAS, showing that it is effective in improving mood and reducing symptoms of depression and posttraumatic stress in caregivers of children receiving a diagnosis of cancer. Significantly, the improved problem-solving skills of caregivers mediated changes in mood, depression, and posttraumatic stress.\textsuperscript{64,65} Further, Bright IDEAS is a psychosocial intervention that teaches problem-solving skills to a nonclinical population when they are under duress. Thus, problem-solving skills training has had wide-ranging applicability based on its successful use in pediatric patients with cancer for school reintegration,\textsuperscript{66} adult patients to enhance overall mood, and caregivers of adult patients with cancer.\textsuperscript{67}

Bright IDEAS was initially developed as a skill-based intervention in the early 1990s for caregivers (primarily mothers) of recently diagnosed patients with childhood cancer. The lightbulb in the logo signifies a sense of optimism (positive orientation) about solving problems that is essential for successful implementation. The letters I (identify the problem), D (determine the options), E (evaluate options and choose the best), A (act), and S (see if it worked) signify the five essential steps of problem-solving.\textsuperscript{30} It is an exemplary intervention that has been developed over three decades and received the designation of one of a select group of Research-Tested Intervention Programs by the National Cancer Institute of the National Institutes of Health (http://rtips.cancer.gov/rtips/). Bright IDEAS has been examined in four large studies, including three that have been multisite RCTs, with well over 1,400 caregivers of recently diagnosed patients with childhood cancer.\textsuperscript{10,63,68} Since 2015, the Bright IDEAS team has been actively disseminating this evidence-based intervention as part of an expansive translational research project.

Briefly, Bright IDEAS has been studied in the following sequence: (1) 1995—the initial study consisting of eight 1-hour individual sessions, according to a detailed protocol, at eight sites with four different languages. Bright IDEAS was acceptable to caregivers (n = 92); problem-solving skills improved, and distress was lessened. Subsequent to this pilot feasibility trial, the Bright IDEAS team conducted a large randomized controlled trial of Bright IDEAS versus usual psychosocial care. Caregivers were randomly assigned to receive Bright IDEAS or usual psychosocial care at seven sites in two different languages and demonstrated that enhanced problem-solving skills mediated decreased negative affectivity (e.g., mood, depression, and post-traumatic stress) in the Bright IDEAS arm (n = 430).\textsuperscript{10} Finally, a second large RCT of Bright IDEAS versus nondirective supportive therapy was reported from seven sites in two different languages. This work demonstrated sustained effects of teaching coping skills compared with providing general support (n = 301).\textsuperscript{63} Finally, the Bright IDEAS group has just initiated another trial comparing Bright IDEAS (face-to-face) versus eBright IDEAS (online) at five sites in two different languages that recently completed accrual (630 enrolled). Analyses are ongoing with pending results.

Based on these findings, particularly in disadvantaged caregivers (e.g., mothers with low socioeconomic status, single, and minority),\textsuperscript{10,68} and the effectiveness of teaching coping skills that have ongoing impact even after formal contact ends, the Bright IDEAS group is currently increasing access by national dissemination of the Bright IDEAS program to more than 90% of the pediatric oncology treatment centers in the United States, supported by a National Cancer Institute grant (R25 CA183725: co-project directors/principal investigators: Noll and Sahler). In efforts to build capacity of Bright IDEAS, they have trained over 220 professionals to date (e.g., PhDs, advanced practice nurses, and social workers) with a study design that includes careful monitoring of dissemination by each trainee in five ways: (1) number of professionals trained (Bright IDEAS trainees); (2) number of pediatric oncology sites with a trained professional; (3) number of ADVANCED Bright IDEAS trainers that are trained (train the trainer); (4) number of workshops provided by the Bright IDEAS trainers; and (5) number of professionals at the sites or regionally who are trained by the Bright IDEAS trainers in providing Bright IDEAS (i.e., success of the train-the-trainer model).

The effectiveness of Bright IDEAS is now well established. However, its adoption into clinical practice has been limited to seven research centers (i.e., less than 5% of all pediatric oncology centers in the United States).\textsuperscript{10,63,70} Although caregivers remain central to cancer care, especially in pediatrics, and data support the link of caregiver support to
patient outcomes, very few interventions have been effectively translated broadly across cancer care. Thus, the translation of well-established interventions, such as Bright IDEAS, which remains exemplar in the childhood cancer care setting, into clinical practice remains a critical challenge for delivering optimal cancer care.

The implementation and evaluation of the dissemination plan for the Bright IDEAS training has been thoughtfully designed with an implementation science expert using two frameworks from implementation science: diffusion theory and Reach, Effectiveness, Adoption, Implementation, and Maintenance. According to a recent review of dissemination and implementation research funded by the National Institutes of Health (2005 to 2012), the frameworks that have been shown to be most commonly used were Rogers’ Diffusion of Innovations model for designing for dissemination and the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework for evaluating intervention efforts. The dissemination of evidence-based practice does not occur spontaneously; passive approaches, such as reliance on scientific publications and websites alone, are largely ineffective in changing clinical practice. Rather, comprehensive, multilevel approaches, incorporating interpersonal interaction through training and role modeling, are more effective. The use of behavioral science frameworks for designing the dissemination process is highly recommended and is currently the strategy being used in the Bright IDEAS dissemination plan. A unique feature of pediatric oncology is that treatment is concentrated among approximately 220 centers within the Children’s Oncology Group. Patients and family caregivers unify to participate in large, multicenter Children’s Oncology Group trials, which has been the backbone and foundation of advancing pediatric cancer care over the years. Based on this model and the knowledge that family caregivers are central to patient outcomes, especially in pediatrics, expanding standards of care, including effective interventions, to support caregivers specifically through diagnosis, treatment, survivorship, and end-of-life in clinical practice is needed.

Based on the literature review, a key implication is the need for transdisciplinary research investigators partnering with clinicians, patients, and family caregivers at the bedside. Further, it remains critical to consider major advances in self-directed technology and societal changes, such as distance/demographics of caregivers, ethnic diversity, aging population, cancer care advances, and dual-earning families (i.e., accounting for more male caregivers with working female caregivers) in designing and developing effective interventions for caregivers of patients with cancer.

**LIMITATIONS**

This review was limited to English-language publications and only included studies published in last 10 years. There is also a possibility of the exclusion of related studies due to limitation of search engines and terms. The definition of caregiving with technology is relatively new and still evolving. Therefore, our definition and approach may not have covered all relevant studies. Given the increased attention to supporting caregivers of patients with cancer and rapid changes of technology, there may be recent studies currently under development or review that were not covered. Because 10 of 18 studies in this review were conducted in last 3 years, we hope future studies would be enhanced with the inclusion of these undiscovered studies.

**CONCLUSION**

Our review shows that there is a current paucity of science (technology-mediated or otherwise) related to helping caregivers of patients with cancer, as well as a standardized approach to improve usability and active adoption of developed interventions. With growing populations and the rising costs of advanced cancer therapy, technology-aided interventions have the capacity to provide effective solutions for families whose lives are affected by cancer. By devising better ways to implement mobile health technology, health care institutions would provide both patients and caregivers with a better-quality health care experience.

### References


Cost, Value, and Financial Hardship in Cancer Care: Implications for Pediatric Oncology

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OVERVIEW

Cancer care in the United States faces a perfect storm: an aging population and expected increased cancer incidence, growing numbers of cancer survivors with ongoing care needs, and continued scientific advancements, offering extraordinary promise at extraordinary cost. How, then, do we as pediatric oncologists engage in the dialogue about cancer cost considerations? The purpose of this article and its accompanying session presented at the 2018 ASCO Annual Meeting is to introduce concepts of cost, value, and financial hardship. In the first section, we will provide an overview of principles of health economics, including components of cost, time horizon consideration, discounting, and methods to calculate incremental cost-effectiveness among therapeutic approaches. We will then introduce the value framework being debated in adult oncology and offer potential opportunities for its application in pediatric oncology. In the second section, we will describe the integration of the cost-effectiveness paradigm in an ongoing pediatric clinical trial, including design and analytic considerations. In the third section, we will shift away from cost to the health care system to cost to the patient, which is also termed “financial toxicity” or “financial hardship,” focusing on the ongoing burden of cost on survivors of childhood cancer. Our goal is to provide our readers with the vocabulary and understanding of this complex and often thorny debate so that they can be active participants and informed advocates for their patients.

Historically and in contrast to medical oncology, the cost of care has not been a dominant theme in pediatric oncology. Explanations for this include the relatively small number of incident and prevalent cases of cancer in children relative to adults, the paucity of emerging new therapies, and the relatively small proportion of total health care expenditures attributable to pediatric oncology. In addition, few health insurance plans include sufficient numbers of childhood cancers to study treatment patterns or the cost of care.

Although the incidence of pediatric cancer has remained relatively stable, the aging of the U.S. population has resulted in increased incidence of cancer for the population overall; this trend is projected to continue. By 2030, it is estimated that nearly 20% of the U.S. population will be at least age 65; the total cancer incidence over that same time period will increase by 45%. Moreover, the number of cancer survivors continues to grow. It is estimated that there are approximately more than 400,000 survivors of childhood cancer and, by 2040, a total of 26.1 million survivors across the entire age continuum. As cancer has become a chronic disease, many survivors continue to have ongoing health issues long after their initial treatment is completed and, as a result, continue to interact with the health care system to manage sequelae of their disease and treatment. Emerging research has described the financial hardship that survivors face and the impact of this burden on their health-related quality of life (HRQL).

On the discovery side, the number of new cancer drugs also continues to grow. In the last year alone, 57 new drugs were approved or had expanded indications; several are actively being investigated in clinical trials, including in pediatric oncology. In August 2017, the U.S. Food and Drug Administration approved the first gene therapy, known as CAR-T cell therapy, for the treatment of pediatric acute lymphoblastic leukemia. Since then, other cell therapies have also been approved with estimated costs ranging from $475,000 to $1.5 million. In addition to actual cost of the therapy, a cascade of costs has been described with this therapy, including supportive care, intensive and extensive hospital care, and potential downstream cancer care. Proponents of these new therapies, particularly for children, point to the promise of lifelong cure, whereas critics raise concerns about the unsustainability of treatments at this price point for patients and their families and for society more broadly.

Although the cell therapies represent the most expensive class of treatments, the cost of all cancer treatment has increased dramatically, and many therapies have price tags of $100,000 or more annually. The unchecked price of...
cancer therapy and continued use of novel therapeutics and diagnostics with little regard to price have contributed to a projected increase in national cancer expenditures over the decade from 2010 to 2020. Based only on population changes during this period, cancer expenditures are projected to increase by 27%, and when costs associated with expensive treatments are considered, cancer expenditures are projected to rise by 39% to 66% during this 10-year period. Concurrently, the excess financial burden to patients also has grown; cost concerns are common among adult survivors of cancer.

In a 2010 survey of members of ASCO, 67% of respondents thought that access to effective treatment should not be influenced by cost. However, 56% said that drug costs influenced their treatment decisions. For 84% of respondents, treatment decisions were also influenced by patients’ out-of-pocket expenses. Despite these concerns, only 42% of respondents reported always or frequently discussing costs with their patients.

Increasingly, professional organizations, patient advocates, and provider groups have called for greater transparency about the cost of care, throughout the care continuum. Frank discussions about upfront and potential downstream costs are needed as patients, their families, and providers make decisions about care. Beginning in 2007, ASCO has directly addressed the rising cost of cancer care by convening a series of task forces, designed to educate oncologists about cost and stimulate timely discussion between patients and providers about potential cost implications of treatment. By 2013, ASCO renamed the task force to “Value in Cancer Care,” which led to the development of a value framework, focusing on toxicity (safety) and clinical benefit (efficacy) in addition to cost (efficiency). To date, most of the ASCO focus has been on adult oncology rather than pediatric oncology.

METHODS OF ECONOMIC EVALUATION

The underlying assumption in economic evaluation is that although demand for services is infinite, societal resources are limited. Therefore, the goal of economic evaluation is to determine which interventions have greater value than others. As noted, one of the most widely used methods to compare interventions is cost-effectiveness analysis (CEA). This method is appropriate when the interventions affect the same health outcome, such as survival in life-years or quality-adjusted life-years (QALYs). In CEA, the incremental costs are divided by the incremental benefits, yielding the incremental cost-effectiveness ratio (ICER). Typically, the costs included in CEA are those directly related to the medical care received (direct costs) or incurred by the patient and family in seeking medical care (e.g., out-of-pocket expenses). Costs associated with informal caregiving, referred to as spillover costs, are not routinely included in cost analyses, likely resulting in an underestimate of total costs for a given intervention, especially in a pediatric population. The perspective of the analysis determines what types of costs are included. Health economists generally recommend that a societal perspective be taken in determining costs under the assumption that money spent on health care is not available to be spent on other societal needs. Because of the complexity of the U.S. health care system with regard to both the purchasing and delivery of health care beyond a single payer or government intervention, other perspectives, such as payer or institution, have also been used.

Costs can be collected directly from the health sector (e.g., hospital billing and administrative claims) or imputed from units of use, obtained from the health record and/or reported by the patient/family. Most administrative data reflect charges (i.e., billed services) rather than true costs and must be adjusted using available institution-specific cost-to-charge ratios. Costs incurred by patients and families can be estimated from cost diaries. Productivity cost can be measured by reduction in work hours, missed days from work, or consumption of benefits (e.g., vacation days and personal time off) or reported work interruption (referred to as presenteeism). Intangible costs, because of pain and suffering, are more challenging to measure and often excluded from cost analysis.

When the denominator in CEA is QALYs, the type of analysis is referred to as cost-utility analysis. QALYs are derived as the product of survival measured in years times the quality of life of those years, measured as a value from 0 to 1, as the product of survival measured in years times the quality of life. Utility can be measured directly or indirectly from validated questionnaires. Costs per QALY for a particular therapy can be benchmarked against other therapies or compared with threshold of $50,000 to $100,000; the cost/QALY ratio for cancer therapy is on average higher than for noncancer therapy. In the United States, use of a threshold generates concerns about rationing, although CEA thresholds are used in other countries in decision-making about treatment coverage.

Although the principles of the dialogue between provider and patient about cost of cancer care are similar, there are key differences between the adult and pediatric populations, the most obvious of which is time horizon. For many children with cancer, the goal of cancer therapy is to restore
health and optimize functioning over decades. An expensive upfront therapy that achieves long-term disease control and prevents future relapse and its associated toxicity may in fact be good value. Similarly, a costly therapy that achieves better palliation and symptoms relief may also be good value for money.

In general, health improvements lag relative to cost, as illustrated in Fig. 1.27 Modeling approaches are generally needed to estimate costs and benefits beyond time horizon of available data. Methodologically, health economists use discounting to adjust the present value of costs and benefits. Outcomes that occur in the near term are more salient than outcomes occurring in the future. This is known as time preference. Typically, a discounting rate of 3% to 5% is recommended for discounting.28

With rising health care costs in cancer care and therapy, decision-makers, including patients, providers, medical systems, and payers, increasingly seek evidence of economic value to evaluate effectiveness of new therapies. In 1996, the panel on cost-effectiveness in health and medicine published a series of recommendations for reporting CEA, defining the components included in both the numerator and denominator of the CEA ratio, the role of time horizon, and use of discounting.29 These recommendations were updated in 2016 to highlight the need for incorporation of both the societal perspective and the health care sector or other decision-makers’ perspectives in analyses, based in QALYs.28 The International Society for Pharmacoeconomics and Outcomes Research developed the first Good Practices guideline for CEA alongside clinical trials in 2005, with an updated report in 2014.30 Although pairing of economic trials to clinical trials has been accomplished in cardiovascular disease, immunization practices, and specific adult cancer settings, there has been no prospective CEA evaluation in a multicenter pediatric oncology trial to date.

A retrospective estimation of inpatient costs by trial arms in a large Children’s Oncology Group (COG) randomized controlled trial (RCT) for acute lymphoblastic leukemia demonstrated the strength of linkage of clinical trial data to controlled trial (RCT) for acute lymphoblastic leukemia in a large Children’s Oncology Group (COG) randomized controlled trial (RCT) for acute lymphoblastic leukemia. Although HL is a very curable in children and adults, long-term sequelae contribute to chronic disease in survivors.36,37 Curative therapy has evolved from large radiation fields as a single modality, to multiagent chemotherapy, to contemporary combined modality therapy. Early success in disease control stunted the search for new therapies or for consideration of endpoints beyond disease-free survival with conventional therapy. In fact, no new pharmacotherapy class had been applied for HL for decades until the advent of the antibody drug conjugate brentuximab vedotin.38 The recognition of late morbidity and mortality from curative therapy has forced consideration of overall survival as a better measurement of treatment effectiveness, whereas disease-free survival remains the endpoint of efficacy with new therapies. In pediatric HL, overall survival remains high because of the availability of effective salvage therapy approaches, but this endpoint fails to capture latent events, late morbidity, the impact of salvage therapy on HRQL, and premature mortality in survivors. Furthermore, the nature and design of interventional clinical trials focus on short-term efficacy of a novel therapy, but are unable to capture the impact on HRQL, survivorship, and financial health in either those who remain disease-free or those who require additional therapy after failure of the initial treatment.

With rising costs of cancer care, cost endpoints are of importance to the multiple stakeholders, including patients, caregivers, providers, payers, pharmaceutical companies, and policy makers.39 Direct and indirect costs of standard therapy have never been studied in pediatric HL. As expensive novel supportive care approaches, such as growth factor use or other supportive care, such as serotonin antagonists for emesis control or novel agents to treat tumor lysis syndrome (e.g., rasburicase),40 Although there has been an increase in application of economic evaluation methods, there has been no prospective incorporation of CEA into a multi-institutional RCT of a standard versus a new oncology therapy in pediatrics.

**THE CLINICAL CONTEXT**

Interestingly, despite rapid advances in novel hematologic therapies, no trial has reported on CEA in upfront treatment of Hodgkin lymphoma (HL). Although HL is a very curable in children and adults, long-term sequelae contribute to chronic disease in survivors.36,37 Curative therapy has evolved from large radiation fields as a single modality, to multiagent chemotherapy, to contemporary combined modality therapy. Early success in disease control stunted the search for new therapies or for consideration of endpoints beyond disease-free survival with conventional therapy. In fact, no new pharmacotherapy class had been applied for HL for decades until the advent of the antibody drug conjugate brentuximab vedotin. The recognition of late morbidity and mortality from curative therapy has forced consideration of overall survival as a better measurement of treatment effectiveness, whereas disease-free survival remains the endpoint of efficacy with new therapies. In pediatric HL, overall survival remains high because of the availability of effective salvage therapy approaches, but this endpoint fails to capture latent events, late morbidity, the impact of salvage therapy on HRQL, and premature mortality in survivors. Furthermore, the nature and design of interventional clinical trials focus on short-term efficacy of a novel therapy, but are unable to capture the impact on HRQL, survivorship, and financial health in either those who remain disease-free or those who require additional therapy after failure of the initial treatment.

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therapies emerge, understanding the cost consequences in treatment success or failure is of great importance. Contemporary clinical trials in advanced-stage HL are an ideal opportunity for inclusion of CEA aims as an a priori reportable study endpoint. The adoption of antibody-drug conjugates (ADC) like brentuximab vedotin that target the biology of the HL Reed-Sternberg cell has been quickly followed by the development of immunomodulatory PD-1 inhibitors. Both promise to minimize the use of conventional chemotherapy or radiation therapy if efficacious. Their long-term effectiveness remains undetermined, however, underscoring the need for planned follow-up for the risk of late effects of brentuximab vedotin or immunomodulatory drugs (e.g., PD-1 inhibitors), given in the growing child/adolescent. History would tell us that this might take decades to unfold.87,40

OPERATIONALIZING CEA ENDPOINTS IN PEDIATRIC ONCOLOGY

COG, in an actively enrolling phase III RCT (NCT02166463), is comparing the efficacy of five cycles of chemotherapy plus brentuximab vedotin and radiation (experimental arm) against five cycles of dose-dense chemotherapy and radiation (standard arm) for children, adolescents, and young adults (age 2–21) with newly diagnosed advanced-stage HL. Although the primary endpoint is 3-year event-free survival, exploratory aims for CEA were designed and embedded. The endpoint for the CEA aim is determination of the ICER between study arms using unit cost and calculated QALYs for the period from diagnosis until 3 years from completion of therapy. Our a priori hypothesis was that the ICER would favor the experimental arm, which uses the novel ADC. Based on the high cost of the ADC ($16,200 per dose and $81,000 for five cycles for a 70-kg patient) and the previously unstudied cost comparison of hematopoietic stem cell transplantation (HSCT) salvage regimens for patients with relapsed or refractory HL,61,62 the trial for advanced-stage HL is an ideal setting to establish a paradigm for pediatric CEA studies. Concurrent aims focus on chemotherapy-associated peripheral neuropathy (CIPN), a specific targeted toxicity and risk in both trial arms, and HRQL to evaluate the functional impact of both and the entirety of the therapy course. Both were captured using patient-reported outcomes (PROs). Self-report of health care use and caregiver burden was also incorporated in this pediatric population. The study aims are independent, yet all part of the a priori design toward the CEA aim embedded in the RCT in keeping with International Society for Pharmacoeconomics and Outcomes Research guidelines.

The trial incorporated mandated completion of PROs at baseline and at key therapeutic points throughout the study for all consenting patients. Although pediatric HL therapy is delivered over 4 days in an outpatient setting by most centers, the dose-dense chemotherapy treatment is associated with toxicity that may require hospitalization for any given cycle.63 Validated instruments of direct and indirect health care costs are completed by parents and youth as age appropriate (Table 1): the Stanford Healthcare Utilization questionnaire’s four items quantify outpatient care (physician’s office and emergency department visits), hospitalizations, and length of hospitalization44,45; the Health Utilities Index 2/36,67 will yield utility weights used to calculate QALYs. Assessments occur at six time points: (1) baseline, prior to initiation of cancer therapy, (2) at two points during scheduled outpatient therapy visits over the 15 weeks of therapy, (3) at completion of therapy, (4) and at 12 and 36 months after completion of therapy. Longitudinal assessment will enable tracking of health care use and QALYs anchored to key therapeutic points across the period of acute treatment and the follow-up period of highest risk for treatment failure in HL.

Clinical trial data of key importance to the CEA include adverse events (AEs) that result in hospitalization and institution-reported data regarding salvage therapy in cases of failure of primary therapy. The pairing of PROs with captured trial data are consistent with the International Society for Pharmacoeconomics and Outcomes Research recommendations for quality CEA studies. Because standard therapy in advanced-stage HL yields event-free survival rates of 75%, the capture of salvage therapy regimens following failure of primary treatment is a key component of CEA in this disease.

Instrument selection, measurement approaches, and planned analyses addressed the need for dyadic data in pediatric populations, combining input from parent proxies and age-eligible youth. Minimizing study burden to patients and parents was also of import in instrument selection. All PROs and self-assessments were available in Spanish and English to maximize generalizability to diverse North American populations. However, the CEA aim and data collection were limited to participants at COG institutions in the United States, because of the difference in payer systems.

The sample size for the CEA aim was determined to detect a clinically meaningful difference of 0.03 utilities between the experimental arm and standard arm. In fact, the sample size necessary is less than 50% of that needed for the primary efficacy aim and accounts for attrition and within-person correlation, given the longitudinal component of the data.

This earlier completion of the CEA accrual will facilitate follow-up time points to be available in a timely fashion relative to closure of full accrual and hence ability to unblind the CEA analysis to study arms.

Feasibility of carrying out the CEA in this trial has included careful inclusion of the CEA study team with the oncologist and the statisticians from the initiation of protocol development. Key CEA team members include pediatric oncologists with HL-specific expertise and expertise in health policy, financial toxicity, and trial design. In addition, a health care economist was a key participant in study inception. Importantly, as the key contributor outcomes depend on self-report by parents and/or youth longitudinally, a central study clinical research associate was engaged to track and ensure return of study assessments across the multi-institution trial. Early study design also involved key stakeholders from the patient

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advocate community, the National Cancer Institute (NCI) Division of Cancer Prevention, and the pharmaceutical partners who manufacture the ADC used in the experimental arm.

As the NCI cooperative group mechanism and funding are focused on the infrastructure, operations, and funding for the parent trial of efficacy, embedded endpoints for good conduct of CEA often need support from external sources. Engagement and funding from stakeholders are key to this process. In our study, funding was sought for study personnel, relational database support, and fees related to use/access of questionnaires and administrative databases (for mapping of AE and International Classification of Diseases, Ninth or Tenth Revision) that will generate the unit costs.

Support in part was garnered from NCI’s Division of Cancer Prevention and Control to provide the support needed for institutions that manage the extra data gathered. External funders included the Leukemia & Lymphoma Society, which has advocacy interests in the HL population. A small amount of funding was proved by Seattle Genetics as pharmaceutical companies to recognize their need for cost-effectiveness endpoints, especially if the primary efficacy margin may not be superior.

### ESTIMATING DIRECT MEDICAL COSTS WITHIN THE RCT

Direct costs will be derived using a combination of the units of health care use reported by parents and the trial reported AEs that result in hospitalization. These events will be identified through the standardized AE reporting used COG trials. Hospitalization can be corroborated and hospital days estimated from the parent report on the Stanford Healthcare Utilization questionnaire. AEs can be monetized by combining diagnostic codes (International Classification of Diseases, Ninth or Tenth Revision) for the AE within the context of HL in administrative databases, such as the Kids’ Inpatient Database, to yield median charges for the AE-associated hospitalization. The most common AE-associated dose-dense chemotherapy regimen used in both arms of the trial is febrile neutropenia. In addition to estimates of

### TABLE 1. Operationalization of Measures Toward a CEA Embedded in a Pediatric RCT

<table>
<thead>
<tr>
<th>PRO Instrument</th>
<th>Rater</th>
<th>Construct(s) Measured</th>
<th>Use in CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics*</td>
<td>P/YA</td>
<td>Family composition, socioeconomic status</td>
<td></td>
</tr>
<tr>
<td>CIPN aim*</td>
<td>P/Y/YA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACT-GOG-NTX</td>
<td>P/Y</td>
<td>Sensory and motor symptoms, function</td>
<td>Intangible cost</td>
</tr>
<tr>
<td>CHRIs-GlobaI</td>
<td>P/Y</td>
<td>Child HRQL</td>
<td>Convert to utility weights</td>
</tr>
<tr>
<td>CEA aim</td>
<td>P/Y/YA</td>
<td>Multiattribute utility weights (QALY adjustment)</td>
<td>ICER</td>
</tr>
<tr>
<td>Stanford HealthCare Utilization*</td>
<td>P/Y</td>
<td>Number of outpatient/inpatient/emergency department visits, length of hospitalization</td>
<td>Direct cost</td>
</tr>
<tr>
<td>Caregiver Work Limitations Questionnaire*</td>
<td>P</td>
<td>Parental absenteeism and presenteesism (caregiver productivity)</td>
<td>Spillover cost</td>
</tr>
</tbody>
</table>

### Rater/Source Data Elements

<table>
<thead>
<tr>
<th>Rater/Source</th>
<th>Data Elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ann Arbor stage*</td>
<td>Institution/CRF</td>
</tr>
<tr>
<td>NCI CTCCE grade ≥3*</td>
<td>Institution/CRF</td>
</tr>
<tr>
<td>Balis grading of pediatric CIPN*</td>
<td>Provider/CRF</td>
</tr>
<tr>
<td>Receipt of RT*</td>
<td>Institution/CRF</td>
</tr>
<tr>
<td>Therapy at relapse*</td>
<td>Institution/CRF</td>
</tr>
<tr>
<td>Study arm*</td>
<td>COG/CRF</td>
</tr>
</tbody>
</table>

The footnotes denote the following time points in RCT:

*Baseline.

*Cycle 2.5.

*End therapy.

*12 months off therapy.

*36 months off therapy.

*Continuous during therapy.

*At relapse.

Abbreviations: CHRIs-Global, Child Health Ratings Inventories-Global Health Scale; CTCCE, Common Terminology Criteria for Adverse Events; FACT-GOG-NTX, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity; P, parent; RT, radiation therapy; Y, youth; YA, young adult.
inpatient costs, the Stanford Healthcare Utilization reports will also enable estimation of all outpatient and emergency department visits. The anticipated cost drivers of initial therapy based on experience with the standard treatment arm for HL include hospitalization for AE and the cost of radiation therapy, which is being delivered based on chemotherapy response regardless of study arm.

At unblinding of the RCT, the cost of brentuximab vedotin can be added to the direct costs; partial doses or dose dropout could be calculated based on trial data. In contrast to the case in adult trials, pediatric studies must estimate whether lower cumulative pediatric doses because of lower weights translate to diminished direct costs for the patients with lower body weight.

Another anticipated large driver of direct cost is the salvage therapy used in the case of treatment failure. Our theory is that superior efficacy in disease-free survival in the experimental arm will translate to lower relapse rate and hence, less need for salvage therapy in that arm. Given that the first line of salvage therapy for advanced-stage HL includes autologous HSCT, we expect that this will be the driver of incremental cost difference between treatment arms. Beyond initial salvage, 50% of patients with HL are at risk for failure after autologous HSCT and will proceed to allogeneic HSCT, and the cost of increased failure on any arm of the trial will be compounded. Study case report forms (CRFs) were constructed to capture the type of relapse therapy given to all participants, hence receipt of HSCT of any type, other chemotherapy or novel agents, or nonprotocol radiotherapy will be captured and monetized.

Currently, the average cost of an autologous transplant is approximately $80,000, whereas the cost of an allogeneic HSCT is about $400,000. In addition to these published estimates, costs of salvage therapy, including HSCT, can be derived from administrative databases, such as the Massachusetts All-Payer Claims database. Additionally, based on the favorable results of the AETHERA trial in adult patients with HL, it is possible that patients can receive up to 16 doses of the brentuximab after autologous HSCT as part of the salvage approach. This would add an additional $259,200 after autologous HSCT, if similar salvage were adopted in pediatrics.

Additional outcomes of interest include the impact of AEs that are not severe enough to cause hospitalization or medical attention but affect patient HRQL, such as CIPN. CIPN will be measured both by clinician grading and PRO and correlated to PROs of HRQL. Differential rates of CIPN or of impaired HRQL may be reflected in lower utility scores, as has been reported with CIPN in patients with breast cancer, and thereby may yield insight into any difference in QALYs between the treatment arms.

Lastly, we examine one dimension of caregiver burden in this pediatric population. The Caregiver Work Limitations Questionnaire measures self-reported limitations of job tasks in working parents. These scores can be translated to costs, which are important from the caregiver and societal perspective.

The incorporation and study of incremental cost in pediatric cancer has lagged other cancers because of delay in the novel drug pipeline to children. In addition, the societal perspective has not mandated such analyses, as the relatively low caseload of pediatric cancer translates to a low portion of the health care bill and because the emotional response to childhood cancer has allowed “exceptionalism” for the discipline. However, with rising costs and the known tradeoffs in the long-term morbidity of curative therapy, CEA and comparative effectiveness are of increasing value to many. The COG trial for advanced-stage HL serves as a proof of paradigm for studying the value of new interventions using PROs to generate QALYs and linked to costs. Successful incorporation and quality execution of CEA methodology in pediatric trials of novel therapies involves stakeholder investment. Dedicated resources contribute to high completion rates of embedded PROs in an RCT and will minimize risk of respondent bias and optimize generalizability of results.

In the aforementioned COG study, we did not attempt to capture out-of-pocket costs or translate the elements of financial hardship in patients with cancer. Nevertheless, patients with cancer and their families in the United States increasingly bear the burden of higher cancer-related costs. For those with health insurance coverage, patient cost-sharing is increasing with higher premiums, deductibles, copayments, and coinsurance rates. Oral cancer therapies are usually included in the specialty tier on prescription drug formularies, in which coinsurance rates of 30% of the drug price are common. Patients and their families without health insurance are responsible for the entire cost of treatment. In addition, the nonmedical costs of cancer care, such as transportation to and from cancer centers, housing, as well as changes to employment and work schedules to accommodate treatment, can be substantial for patients with pediatric cancer and their families.

Elevated costs of medical care can continue long after the completion of cancer treatment, reflecting late and lasting effects of treatment and increased risk of developing other conditions. A number of studies have shown that adult survivors of cancer have higher out-of-pocket spending than individuals without a cancer history, even many years after diagnosis or the completion of treatment. Similarly, adult survivors of cancer are more likely than adults without a cancer history to report productivity losses, including the inability to work or pursue usual activities, more days lost from work, reduction in work hours, or days spent in bed. Productivity losses are also common for adult survivors of childhood cancers. Compared with those without a cancer history, adult survivors of childhood cancers were less likely to be employed (54.3% vs. 69.6%), more likely to be unable to work because of health (18.7% vs. 7.1%), and have spent more days in bed because of health in the past 12 months (14.6 days vs. 4.1 days), after adjusting for the effects of sociodemographic characteristics and comorbidity burden. The excess annual per capita productivity loss was estimated to be $5,086 for adult survivors of childhood
cancer. Survivors of childhood cancers also face short-term and lasting financial hardship.58

**WHAT IS FINANCIAL HARDSHIP?**

Research addressing financial hardship in adult survivors of cancer has increased dramatically in the past decade.59-61 These studies frequently use different terminology, including financial toxicity, financial burden, financial distress, and economic hardship, but generally reflect the same underlying concepts, including material, psychological, and behavioral domains (Fig. 2). Material conditions are typically measured as out-of-pocket expenses for medical costs, productivity losses, reduction in income, depletion of assets, medical debt, trouble paying medical bills and other necessities, and bankruptcy.59,62 The majority of studies of financial hardship in adult survivors of cancer measure material measures and show that as many as half of adult survivors of cancer report some form of material financial hardship.59 Psychological response is typically measured as stress, distress, and worry about paying bills for cancer, its treatment, and lasting effects of treatment or concerns about wages and wage loss associated with cancer. As many as 64% of adult survivors of cancer report some form of psychological financial hardship.59 Coping behaviors that survivors adopt in the face of increased household expenditures and related distress are typically manifested by delaying or foregoing medical care and nonadherence to prescription medications for cancer and other conditions. Up to 45% of adult survivors of cancer report some form of behavioral financial hardship.59

Substantially fewer studies address financial hardship in adult survivors of pediatric cancers and their families. In one of the few studies of adult survivors of childhood cancers participating in the Childhood Cancer Survivor Study, spending a higher proportion of income on out-of-pocket health care costs was significantly associated with problems paying medical bills (material hardship), worry about affording health insurance (psychological hardship), and deferring care, skipping tests, treatment, or follow-up or taking a smaller dose of medication than prescribed (behavioral hardship).58 Mean time since diagnosis in the sample was greater than 30 years, suggesting the lasting effects of financial hardship for survivors of childhood cancers.

Estimates of the prevalence of different aspects of financial hardship in survivors of cancer vary widely depending on differences in populations studied, including age distribution, cancer type(s), stage of disease at diagnosis, number and types of treatment(s), time since diagnosis, time since last treatment, comorbidity burden, socioeconomic characteristics, and health insurance coverage. Measures of financial hardship, including domain of hardship, whether measures are specific to cancer care or medical care more generally, also vary, as do whether estimates considered or adjusted for survivor sociodemographic and clinical characteristics. As a result, comparisons of estimates of prevalence of financial hardship between studies of adult and pediatric survivors of cancer cannot be easily made, but health consequences of hardship and risk factors for hardship are likely to be similar.

**WHAT ARE THE HEALTH CONSEQUENCES OF FINANCIAL HARDSHIP?**

In the few studies that have evaluated the adverse health consequences of financial hardship, survivors of cancer with hardship have poorer HRQL than those without hardship.63-65 They are also more likely to report increased symptom burden and pain,63 worse mental and physical health and satisfaction with social activities and relationships,64 and increased depression and cancer-related worries when compared with survivors of cancer without financial hardship.65 In a study that linked cancer registry data to bankruptcy filings, survivors who filed for bankruptcy had greater risk of mortality than those who did not file for bankruptcy, even after considering key patient characteristics, such as stage, age, race, marital status, initial treatment, and area-level income.66 Findings were robust in sensitivity analyses, including those that restricted the sample to an early stage of disease at diagnosis.

**WHAT ARE RISK FACTORS FOR FINANCIAL HARDSHIP AND HOW CAN THEY BE ADDRESSED?**

In the following section, we describe a framework that can be used to identify risk factors associated with financial hardship and approaches for developing and tailoring interventions to mitigate its impact (Fig. 3).59 The framework has multiple hierarchical levels, starting with survivors of cancer and their families/caregivers in the center and then surrounded by provider and provider teams, organizational, local community, and state and national policy levels. At the patient and family level, financial hardship in adult survivors of cancer varies by cancer site,67,68 type(s) of treatment, time since last treatment, and/or time since diagnosis.59,60,69

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**FIGURE 2. Factors at Multiple Levels Associated With Financial Hardship**

- National Health Policy Environment
- State Health Policy Environment
- Local Community Environment
- Organization and/or Practice Setting
- Provider Terms
- Patient and Family

Risk of Financial Hardship

---
Socioeconomic factors are associated with greater risk of financial hardship including lower household income and/or educational attainment, minority race/ethnicity, and lack of health insurance.68-71 Because the late effects of cancer treatment can limit employment, lost wages and loss of employment-based health insurance can increase the risk of financial hardship.59,71 The uninsured, who are responsible for all costs of medical care, may have even higher barriers to receipt of recommended care and report greater levels of financial hardship.59 Thus, with higher risk of financial hardship among racial/ethnic minorities, the poor, and the uninsured and increasing costs of cancer care, historical disparities in outcomes for these populations may widen in the future. Evaluating the role of financial hardship in health disparities will be important for future descriptive research and informing intervention development.

Informal caregivers, including spouses and partners, siblings, parents, and children, also experience productivity losses and financial hardship.72 This is an especially important topic for survivors of pediatric cancer, who may require care for late effects of their therapy and may be accompanied by multiple caregivers, particularly during active treatment in their childhood years.

At the provider level, professional organizations such as ASCO have highlighted the important role of oncologists in discussions about the out-of-pocket costs of cancer care.18 Oncologists generally agree about their responsibility for this discussion; however, these discussions are rare, and many oncologists feel uncomfortable engaging in these discussions.73 Several studies are exploring the role of other members of the health care team for discussing cost of care and risk of financial hardship and the role of financial navigators in minimizing financial hardship.74 This will be an important area for additional research.

Little research on risk factors for financial hardship has been conducted at the organizational levels of health care systems and practices or community, but more evidence is available at the state and national levels. These levels are especially relevant because health insurance policies are generally enacted in states or nationally. Components of the Affordable Care Act (ACA), including introduction of the Marketplace coverage and Essential Health Benefit standards, elimination of pre-existing condition exclusions and lifetime and annual coverage limits, and expansion of Medicaid eligibility in some states and dependent coverage expansion, allowing young adults to remain covered under a parent’s health insurance until age 26 have the potential to minimize the impact of financial hardship for survivors of cancer.

Several studies have demonstrated positive effects of the ACA on insurance coverage, access to care, and earlier stage of disease at diagnosis25-78; however, few studies have explored the impact of the ACA on financial hardship in survivors of cancer. Survivors of pediatric cancer may be especially vulnerable to changes in health insurance coverage policies; a nationally representative survey reported that survivors were more likely to have Medicaid coverage than their counterparts without a cancer history (27% vs. 15%).55 Additionally, adult survivors of childhood cancer are more likely to report health insurance coverage denials than their siblings without a cancer history.79 Evaluation of the effects of different aspects of insurance coverage and the ACA specifically is ongoing.

The ACA also enhanced health insurance coverage for clinical trial participants—health plans or insurers cannot keep patients from joining a clinical trial, limit or deny coverage of routine care, or increase costs because patients join a trial. Limited research has addressed the effects of these clinical trial provisions, and evidence is mixed. One study reported higher insurance clearance rates for early-phase oncology trials in a single institution following implementation of the ACA compared with before implementation,80 whereas the other study reported insurance coverage denials and delays in trial enrollment following implementation of the ACA.81 Future research evaluating the effects of the ACA in pediatric cancer trial enrollment will be important.

The formal study of cost associated with pediatric cancer care has lagged other cancers because of delay in the novel drug pipeline to children and the relatively small number of patients with childhood cancer within the same health care system. In addition, the societal perspective has not mandated such analyses as the relatively low caseload of pediatric cancer translates to a low portion of the health care bill and because the emotional response to childhood cancer has allowed “exceptionalism” for the discipline. However, with rising costs and the known tradeoffs in the long-term morbidity of curative therapy, CEA and comparative effectiveness may be used to more fully understand the potential tradeoffs of care decisions. Going forward, it will also be important to understand how patient and disease characteristics, disease...
response, toxicity, and preferences influence CEA results and inform value-based decision-making. Rising costs of cancer care and increasing patient cost sharing make the study of financial hardship in survivors of childhood cancers increasingly important. Better measurement of the prevalence of financial hardship, including material, psychological, and behavioral domains, and risk factors in adult survivors of childhood cancers will inform the development of effective interventions to minimize its effects. Although little is known about the long-term adverse health consequences of financial hardship, research in adults suggests that it will be a critical area for future research in children. Simultaneous consideration of the multiple hierarchical levels that influence hardship—patient and family, provider and provider teams, organizational, local community, and state and national policy levels—will inform this work. As described in this review, these key concepts of cost, value, and financial hardship are critical to the ongoing dialogue about the cost and consequences of pediatric cancer in the United States.

References


PROFESSIONAL DEVELOPMENT
MURALI ET AL

From Burnout to Resilience: An Update for Oncologists

Krithika Murali, MBBS, Vicky Makker, MD, James Lynch, MD, and Susana Banerjee, MBBS, PhD, FRCP

OVERVIEW

Physician burnout remains a highly complex and topical issue. The negative impact of burnout on physicians, patients, and institutions has become increasingly apparent. Globally, a multitude of professional bodies and organizational leaders are giving this important subject much-deserved attention. In this review, we provide a summary of the latest evidence, with a focus on solutions and future strategies, while incorporating our own perspectives as practicing oncologists.

Burnout is a work-related stress syndrome that is particularly prominent in human services occupations such as health care.\textsuperscript{1,2} The onset of burnout can be insidious, thwarting early recognition, but it is not an irreversible event. In contrast to depression, symptoms of burnout tend to resolve with an improvement in the work environment consistent with its close occupational alignment.\textsuperscript{2,3} Although burnout is not formally diagnosed as a clinical disorder, it was included in the 10th revision of the \textit{International Statistical Classification of Diseases and Related Health Problems} as a result of its substantial personal health impact.\textsuperscript{4}

DEFINITION AND MEASUREMENT OF BURNOUT

The 22-item Maslach Burnout Inventory–Health Services Score was developed in the United States in the 1980s and is the most widely used and validated assessment tool for self-reported symptoms of burnout.\textsuperscript{2,5,6} The Maslach Burnout Inventory consists of three domains. High emotional exhaustion and depersonalization correlate with higher degrees of experienced burnout, as does diminished personal accomplishment.\textsuperscript{2,5} This triad is currently the most commonly cited definition of burnout. Maslach recommends analyzing the individual domain scores as continuous data where possible or as categorical data with defined cut-off scores (low, moderate, or high burnout) being an alternative.\textsuperscript{2,7} In addition, single-item measures of emotional exhaustion and depersonalization from the full Maslach Burnout Inventory have been validated as accurate proxy measures of burnout in larger surveys.\textsuperscript{8-13}

The more recently developed Copenhagen Burnout Inventory is another occupational burnout measure that is being increasingly used.\textsuperscript{14,15} It is composed of three scales assessing personal burnout, work-related burnout, and client-related burnout\textsuperscript{15} (Sidebar 1). The Copenhagen Burnout Inventory was initially validated in the PUMA study (Project on Burnout, Motivation and Job Satisfaction), a Danish longitudinal study of burnout in human service sector employees.\textsuperscript{15} The Copenhagen Burnout Inventory was developed to create an alternative questionnaire that was more applicable to a broader range of occupations, was more acceptable within the Danish sociocultural context, and remained in the public domain instead of requiring commercial distribution.\textsuperscript{15} The development of alternative measures to the Maslach Burnout Inventory should be welcomed because it encourages more accurate assessment of burnout in different sociocultural contexts.\textsuperscript{16}

PREVALENCE

Rather than the absolute prevalence rates alone, it is the assessment of longitudinal trends and exploration of associated factors that is often of greater value, as comparison of burnout rates between different eras and sociocultural contexts is difficult.\textsuperscript{16} Furthermore, there is substantial variability in the way researchers have assessed physician burnout,\textsuperscript{17-19} which contributes to considerable variation in its measured prevalence.\textsuperscript{7} Nonetheless, burnout is a consistent problem across a range of medical and surgical specialties.\textsuperscript{20-27} Physicians report significantly higher rates of burnout than professionals in other fields, and this begins while in medical school.\textsuperscript{28} Caring predominantly for patients with terminal illness in a rapidly evolving scientific field is challenging. Although physicians provide cancer care as part of a multidisciplinary team, evidence suggests that cancer physicians experience higher rates of burnout than other nonphysician members of the team.\textsuperscript{29} A recent systematic review and meta-analysis of burnout prevalence in oncologists found that of 4,876 pooled participants from 17 published studies, 32% had high burnout.\textsuperscript{30} Recent national U.S. surveys have found a 45% burnout prevalence rate...
among oncologists.1 This is comparable with the average rate among U.S. physicians.10 There is some suggestion that burnout rates among oncologists may even be lower than more frontline medical specialties such as general internal medicine, family medicine, and emergency medicine.10,28,32,33 Other studies conducted globally have shown burnout prevalence in oncologists ranging from 20% to 70%.34-44 A recent burnout study of oncologists in Europe who were age 40 and younger showed a higher than average burnout rate of 71%.34 The higher rates shown in the European Society for Medical Oncology Young Oncologists Committee Burnout Survey may be attributable in part to its focus on a high-risk population,34 greater openness toward reporting burnout, as well as rising rates of burnout both within medicine20,34-36 and on a population level.20,34, We provide a summary of key burnout prevalence studies in oncologists in Table 1.

CONSEQUENCES
The personal and professional consequences of burnout are profound.3,46 Physician burnout has a negative impact on patient care,47,48 including increased medical error,47,49-51 diminished empathy and altruism,13 and reduced patient satisfaction52,53 and confidence.54 As demand for oncologists continues to grow, burnout has the potential to exacerbate projected workforce shortages55,56 through a concerted reduction in time dedicated to patient care57 and overall work hours or through early retirement.31,51,58 This perpetuates a vicious cycle because increasing demands in the context of decreasing resources will perpetuate workplace strain, as highlighted by the job demands-resources theory.59 The annual productivity loss in the United States attributable to burnout is substantial,60-62 as is the cost of replacing a physician who retires early or leaves the profession.28,63 Burnout also has notable mental and physical health consequences. The risk of alcohol misuse, suicidal ideation, and depressive symptoms significantly increases in surgeons and physicians when burnout is present.11,64,65 In addition, burnout is associated with multiple chronic health conditions,66 an increased risk of motor vehicle accidents,67 and lower physical quality of life.68

RISK FACTORS
Diverse personal, professional, and organizational factors have been associated with physician burnout. These have predominantly been identified through observational or cross-sectional studies. Although causality cannot be inferred, we have distilled these findings into three key themes (Table 2).

Workplace Factors
Oncologists in the United States work more hours annually than a number of other medical specialties.69 Increased work hours are significantly associated with burnout.26,66 Additional professional risk factors that have been associated with burnout include increased administrative workload,36,48,70,71 increased number of hours in direct patient care31,36,70 (with one study showing a 20%–40% higher risk of burnout with each additional 10 hours spent seeing patients31), higher patient caseload,36,44,70 and a reduction in time in meaningful professional activities36,66 such as research68 and educational tasks.36,70

The perception of time pressure is associated with burnout irrespective of quantitative workload or type of work activity.53,71-73 The substantial erosion of physician autonomy in the modern medical era,48,74 with clerical burden often outweighing time spent in direct patient care,75,76 has been associated with higher burnout. Lack of control over work hours in an international cohort of pediatric oncologists79 or over the delivery of medical care for transplant surgeons was associated with higher rates of burnout irrespective of workload.77,78 Medical oncologists have a higher than average risk of medical malpractice litigation.79 Stressful professional experiences such as malpractice litigation80 and medical errors47 can increase the risk of burnout. In addition, delivering bad news to patients can contribute to burnout among oncologists who feel inadequately trained in communication skills.81

Impaired Work-Life Balance
Increased work hours, increased administrative tasks, and lack of autonomy can impair work-life balance. A study of
U.S. oncologists suggests that satisfaction with work-life balance is among the lowest of all medical specialists.57 Having inadequate quality time away from work can independently contribute to burnout and stress,21,34,57,78 including inadequate vacation time34,37 or insufficient time for hobbies.37 Each additional hour per week spent on work-related tasks while at home increases the risk of burnout.31 Similarly, accessing work-related emails and electronic medical records after hours is also associated with higher rates of burnout.82,83 Poor work-life balance is also associated with conflicts at home,84,85 which disproportionately impacts women.84

Demographic Factors
Younger age and being an early career oncologist has consistently been associated with higher rates of burnout in a number of studies.24,26,31,39,42,68,81,86,87 A mismatch between the career expectations of oncology fellows and professional reality has the potential to exacerbate the situation.42 Living alone has been identified as a risk factor for burnout34,37 as well as a sense of loneliness,34 highlighting the importance of support from one’s friends, family, spouse, and colleagues in burnout prevention.88 Lack of access to support services in the workplace has also been associated with burnout among oncologists.34,39

In the European Society for Medical Oncology Young Oncologists Committee Burnout Survey, region of practice had a notable impact on burnout risk. The highest burnout prevalence (84%) was seen in Central Europe (including Hungary, Romania, and Poland) and the lowest rate (52%) was seen in Northern Europe/British Isles (including Scandinavian nations and the United Kingdom).34 These regional divisions were based on United Nations categorization. Because each nation in Europe is composed of diverse health, sociocultural, and economic systems, this is a finding that warrants further study.

A number of studies have also identified female sex as a risk factor for burnout in oncologists, although this association has not been maintained on multivariate analysis.38,39,41,68 These findings should encourage us to investigate other confounding factors that may disproportionately affect women. For instance, the Stanford “time bank” intervention rewarded usually unrecognized activities, such as serving on committees, with in-home support services (e.g., meal delivery and cleaning services). This program was predominantly used by female faculty members. Although the pilot

### Table 1. Summary of Key Oncology Burnout Prevalence Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Region</th>
<th>Period</th>
<th>Sample Size</th>
<th>Population</th>
<th>Burnout Measure</th>
<th>Overall Burnout (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whippen and Canellos</td>
<td>United States</td>
<td>1990</td>
<td>598</td>
<td>Oncologists</td>
<td>Survey specific</td>
<td>56</td>
</tr>
<tr>
<td>Allegra et al</td>
<td>United States</td>
<td>2003</td>
<td>1,740</td>
<td>Oncologists</td>
<td>Survey specific</td>
<td>61.7</td>
</tr>
<tr>
<td>Glasberg et al</td>
<td>Brazil</td>
<td>2004–2005</td>
<td>102</td>
<td>Medical oncologists</td>
<td>MBI</td>
<td>68.6</td>
</tr>
<tr>
<td>Blanchard et al</td>
<td>France</td>
<td>2009</td>
<td>204</td>
<td>Oncology/hematology residents</td>
<td>MBI</td>
<td>44</td>
</tr>
<tr>
<td>Roth et al</td>
<td>International</td>
<td>2010</td>
<td>410</td>
<td>Pediatric oncologists</td>
<td>MBI</td>
<td>38</td>
</tr>
<tr>
<td>Mordant et al</td>
<td>Europe</td>
<td>2010</td>
<td>404</td>
<td>Surgical oncology trainees</td>
<td>Survey specific</td>
<td>25</td>
</tr>
<tr>
<td>Rath et al</td>
<td>United States</td>
<td>2013</td>
<td>436</td>
<td>Gynecology oncologists</td>
<td>MBI</td>
<td>32</td>
</tr>
<tr>
<td>Shanafelt et al</td>
<td>United States</td>
<td>2012–2013</td>
<td>1,490</td>
<td>Oncologists</td>
<td>MBI</td>
<td>44.7</td>
</tr>
<tr>
<td>Shanafelt et al</td>
<td>United States</td>
<td>2013</td>
<td>1,345</td>
<td>Oncology fellows</td>
<td>MBI</td>
<td>34.1</td>
</tr>
<tr>
<td>Leung et al</td>
<td>Australasia</td>
<td>2013</td>
<td>220</td>
<td>Radiation oncologists</td>
<td>MBI</td>
<td>37.1</td>
</tr>
<tr>
<td>Banerjee et al</td>
<td>Europe</td>
<td>2013–2014</td>
<td>737</td>
<td>Oncologists age 40 or younger</td>
<td>MBI</td>
<td>71</td>
</tr>
<tr>
<td>Mampuya et al</td>
<td>Japan</td>
<td>2015–2016</td>
<td>87</td>
<td>Radiation oncologists</td>
<td>MBI</td>
<td>20.6</td>
</tr>
</tbody>
</table>

Abbreviation: MBI, Maslach Burnout Inventory.
Adapted from Murali and Banerjee.89

### Table 2. Risk Factors for Burnout

<table>
<thead>
<tr>
<th>Workplace Factors</th>
<th>Impaired Work-Life Balance</th>
<th>Demographic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased work hours</td>
<td>Completion of work tasks at home</td>
<td>Younger age</td>
</tr>
<tr>
<td>Increased patient contact</td>
<td>Inadequate quality time off (e.g., vacation, hobbies)</td>
<td>Early career</td>
</tr>
<tr>
<td>Increased clerical burden</td>
<td>Work-home conflict</td>
<td>Social isolation</td>
</tr>
<tr>
<td>Time pressure</td>
<td></td>
<td>Country of practice</td>
</tr>
<tr>
<td>Decreased autonomy</td>
<td></td>
<td></td>
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<tr>
<td>Stressful professional event</td>
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</tbody>
</table>
program was successful in improving staff support, it also starkly highlights different social pressures relating to gender.28

PROTECTIVE FACTORS: RESILIENCE, MINDFULNESS, AND MEANING

A number of individual-focused interventions to reduce burnout revolve around the principles of resilience, mindfulness, and promotion of meaning. It is worth reflecting on each of these concepts more deeply. Resilience is potentially a protective factor against burnout. The psychobiological foundations for individual resilience were extensively discussed by Hlubocky et al46 in 2016. Although definitions and ways of measuring resilience can vary, positive adaptation in the face of adversity demonstrates resilience.48,89-91 Resilience is associated with lower burnout levels92,93 and can mediate the relationship between burnout and mental health.94 Nonetheless, it is difficult to translate the promotion of a relatively intrinsic trait such as resilience into an intervention.84 However, it has been noted that self-compassion and mindfulness is often a core tenet of resilience95,96 and can potentially be taught.64 Finding meaning in work, as well as intrinsic motivating factors such as having a sense of calling, also appears to protect from burnout.26,97-99 However, the same research that showed a career and life satisfaction increase as meaningful work hours increased did so only up to a certain point (7.5 hours per day) beyond which it declined, likely as a result of overwork.97,98 There is evidence to suggest that doctors derive tremendous satisfaction from their career.100 and have higher resilience than the general population.101 Discussion of intrinsic traits is not an opportunity to apportion individual blame. Rather, it serves as a reminder that erosive systemic factors can result in resilient and committed physicians feeling burned out.

SOLUTIONS

Key publications have reviewed the solutions that have already been implemented to reduce burnout.102,103 These interventions have been individual-focused, organizational, or mixed strategies. Structural or organizational interventions have generally been more effective at reducing overall burnout than physician-focused strategies, although the latter were still found to be beneficial.102,103 We summarize below key organizational and individual interventional strategies.

Individual-Focused Strategies

Multiple studies have evaluated the benefit of facilitated and nonfacilitated small group curricula,104-110 stress management training,111,112 exercise/self-care programs,113,114 counseling/reflective practice,109,115,116 and Balint group training, demonstrating varied results (Sidebar 2).102,103 Mindfulness practice and mindfulness-based stress reduction has been shown to have multiple benefits,117-119 including some evidence of reduction in overall burnout.120,121 A 2014 systematic review and meta-analysis of interventions to reduce burnout in physicians showed promise for cognitive, behavioral, and mindfulness-based interventions.112 West et al105 conducted a randomized controlled trial of 74 internal medicine physician volunteer participants in a U.S. hospital between 2010 and 2012, which involved participation in 19 fortnightly, facilitated small-group discussion groups over 9 months conducted during employer-provided protected time. These groups incorporated elements of mindfulness, reflection, and experience sharing as well as structured learning modules that covered topics such as medical error. Participants in the study intervention arm showed significantly reduced rates of depersonalization compared with participants in the trial control arm, but overall burnout rate differences were small.105

SIDEBAR 2. Vicky Makker, MD, Memorial Sloan Kettering Cancer Center, Discusses ASCO’s Pilot to Build Primary Resiliency

In 2016, ASCO partnered with palliative care physicians to address burnout and develop methods to help build primary resiliency in medical oncology fellows. From this collaboration arose a pilot training program based on cognitive behavioral therapy approaches. The goal of this training was to define how individual resilience skills can be learned, how workplace engagement can be maximized, feasibility of the curriculum, and assessment of fellow receptivity. Baseline and post-training data were gathered on burnout and resilience using standard surveys. First-year fellows were targeted in four institutions. The pilot program consisted of eight, 1-hour, module-based training sessions. Each module addressed a specific resilience skill, including finding the resilience zone; recognizing cognitive distortions, mindfulness, and self-compassion; finding healthy boundaries; and keeping purpose in view. Sessions occurred weekly, biweekly, or monthly and were led by a myriad of professionals including program directors, social workers, psychologists, and palliative and integrative medicine specialists. Data from the pilot program are being reviewed, but based on positive initial feedback, ASCO is preparing to launch year 2 of this program in 2018. The program will be expanded to include up 16 institutions. Additional data on burnout and the program impact will be collected. Given that the incidence of burnout is alarmingly on the rise, such endeavors are critical to promoting a change in culture, lessening the stigma associated with burnout, instilling skills that foster primary resiliency, and teaching fellows how to recognize signs of burnout throughout their career. But, clearly, much work remains, and combating this epidemic will necessitate both individual-directed and also organization-based strategies.
Although communication skills training is now a routine part of the oncology training curriculum in many countries, an important Cochrane systematic review and meta-analysis of communication skills training for health care professionals working with patients with cancer showed no notable benefit with regard to health care professional burnout, patient satisfaction, patient mental or physical health, or perception of the health care professionals’ communication skills. Of note, studies included in this Cochrane review were not restricted to physician participants alone.

Organizational Strategies
Despite the preponderance of studies on individual-focused interventions, strategies that involve work unit or wider organizational change have demonstrated greater success.
in reducing overall burnout (Sidebar 3). In a review by West et al, six cohort studies assessed the impact of work hour restrictions on overall burnout after the Accreditation Council for Graduate Medical Education–mandated 80-hour week restrictions were introduced in the United States in July 2003. Although a range of results were noted, these six cohort studies showed a notable pooled overall burnout reduction from 62% to 50% among residents. Innovative programs such as the APEX (ambulatory process excellence) program at the University of Colorado, which trained health care assistants to allow clinicians to focus on the most skilled aspects of patient consultation in a distraction-free environment, reduced clinician burnout rates from 53% to 13%. The introduction of APEX in the Department of Family Medicine also improved outcomes such as vaccination coverage and cancer screening tests because health care assistants were able to comprehensively complete preventative tasks.

Another innovative primary health care–based initiative in Portland, Oregon, involved the inclusion of physician well-being as a key organizational performance indicator, regular objective survey-based monitoring of well-being, and responsive workplace quality improvement projects and resulted in a notable reduction in burnout. Workplace and organizational culture has a substantial impact on burnout, as do the leadership qualities of physician supervisors.

**CONCLUSION**

In 2016, chief executive officers from major health organizations in the United States pledged support for the promotion of physician well-being through constructive steps including a robust process for measuring outcomes. Because only a minority of wellness programs currently evaluate the effectiveness of their interventions, such transparency and accountability may herald a new wave of bolder initiatives that eschew tokenism. Structural change is also being instigated by powerful institutional bodies. In January 2017, the U.S. National Academy of Medicine, in collaboration with the Association of American Medical Colleges and the Accreditation Council for Graduate Medical Education, launched the ambitious national Action Collaborative on Clinician Well-Being and Resilience. This initiative has received overwhelming support and four clear collaborative streams have been delineated to promote evidence-based recommendations and key stakeholder engagement. The academy has also provided a comprehensive model for understanding the complex nature of physician burnout in which the patient sits firmly at its center (Fig. 1), reminding us of our primary fiduciary responsibility. By highlighting the importance of the physician-patient relationship, this model underscores the reality that when physicians are in distress, it is not only practitioners but also patients who suffer. The incorporation of physician well-being into the recently revised Declaration of Geneva marks a new global consensus. Physician burnout needs to remain on the agenda and requires ongoing, collective action. In this regard, the importance of the visibility and conversational platform provided by professional bodies, such as ASCO and European Society for Medical Oncology, can never be underestimated.

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**TABLE 3. Effective Approaches Reported Through the American Medical Association STEPS Forward Program**

<table>
<thead>
<tr>
<th>Organizational Strategies</th>
<th>Physician Support</th>
<th>Operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chief wellness officer with wellness committee</td>
<td>Compensation plans including wellness</td>
<td>Address chaotic workplace</td>
</tr>
<tr>
<td>Culture of wellness rather than dealing with burnout</td>
<td>Dinners with colleagues paid by organization</td>
<td>More scheduling control given to clinicians</td>
</tr>
<tr>
<td>Annual wellness surveys</td>
<td>Mindfulness-based stress reduction</td>
<td>Flexible schedules for dealing with family responsibilities</td>
</tr>
<tr>
<td>Wellness as quality indicator</td>
<td>Ensure at least 20% of time spent in meaningful work</td>
<td>Improve workflow efficiency</td>
</tr>
<tr>
<td>Shared accountability for workplace wellness</td>
<td>Collaborative for healing and renewal in medicine (charm)</td>
<td>Reduce clerical burden of electronic health records</td>
</tr>
<tr>
<td>Regular engagement with responsive leadership indicators</td>
<td>Recognize compassionate practitioners</td>
<td>Support team-based care with appropriate staff</td>
</tr>
<tr>
<td>Track business case for wellness</td>
<td>Empower small units to evaluate and improve</td>
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<tr>
<td>Decentralize and allow flexibility at unit levels</td>
<td>Provide onsite exercise, showers, healthy food, and coffee</td>
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<tr>
<td>Empower and encourage rather than design and deploy</td>
<td>Create space for collaboration and collegiality</td>
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<tr>
<td>Establish efficient communication platform</td>
<td>Physician health program as part of health care package</td>
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<tr>
<td>Resource a wellness infrastructure and support</td>
<td>Finding meaning in medicine groups</td>
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![Figure 1](https://example.com/fig1.png)

**Fig. 1.** Academic model for understanding the complex nature of physician burnout in which the patient sits firmly at its center.
FIGURE 1. Factors Affecting Clinician Well-being and Resilience

This conceptual model depicts the factors associated with clinician well-being and resilience; applies these factors across all health care professions, specialties, settings, and career stages; and emphasizes the link between clinician well-being and outcomes for clinicians, patients, and the health system. The model should be used to understand well-being, rather than as a diagnostic or assessment tool. The model will be revised as the field develops and more information becomes available. Subsequent layers of the model, and an interactive version of the model, are in development in conjunction with the Action Collaborative’s other working groups and will be made available shortly.

EXTERNAL FACTORS
SOCI-CULTURAL FACTORS
- Alignment of suicidal expectations and clinicians’ role
- Culture of safety and transparency
- Discrimination and overt and unconscious bias
- Media portrayals
- Patient behaviors and expectations
- Political and economic climates
- Social determinants of health
- Stigmatization of mental illness

REGULATORY, BUSINESS, & PAYER ENVIRONMENT
- Accreditation, high-stakes assessments, and publicized quality ratings
- Documentation and reporting requirements
- UPR policies and compensation issues
- Initial licensure and certification
- Insurance company policies
- Litigation risk
- Maintenance of licenses and certification
- National and state policies and practices
- Reimbursement structures
- Shifting systems of care and administrative requirements

ORGANIZATIONAL FACTORS
- Balanced scorecard
- Congruent organizational mission and values
- Culture, leadership, and staff engagement
- Data collection requirements
- Diversity and inclusion
- Level of support for all healthcare team members
- Professional development opportunities
- Scope of practice
- Workload, performance, compensation, and value distributed to work elements

LEARNING/PRACTICE ENVIRONMENT
- Autonomy
- Collaborative vs. competitive environment
- Curriculum
- Health IT: Interoperability and usability/Electronic health records
- Learning and practice setting
- Mentorship
- Physical learning and practice conditions
- Professional relationships
- Student affairs policies
- Student-centered and patient-centered focus
- Team structures and functionality
- Violence, safety, and violence

INDIVIDUAL FACTORS
HEALTH CARE ROLE
- Administrative responsibilities
- Alignment of responsibility and authority
- Clinical responsibilities
- Learning/learner stage
- Patient population
- Sexuality-related issues
- Student/frame responsibilities
- Teaching and research responsibilities

PERSONAL FACTORS
- Inclusion and connectivity
- Family dynamics
- Financial stress/economic vitality
- Flexibility and ability to respond to change
- Level of engagement/connection vs. meaning and purpose in work
- Personality traits
- Personal values, ethics, and morals
- Physical, mental, and political well-being
- Relationships and social support
- Sense of meaning
- Work-life integration

SKILLS AND ABILITIES
- Clinical Competency/level of experience
- Communication skills
- Coping skills
- Delegation
- Empathy
- Management and leadership
- Mastering new technologies and proficient use of technology
- Mentorship
- Optimizing work flow
- Organizational skills
- Resilience
- Teamwork skills

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GENETIC TESTING FOR CANCER
Cancer is essentially a genetic disease, in that alterations to DNA, including mutations, amplifications, deletions, and translocations, change a gene’s normal function to promote growth, survival, and metastasis. All cancers harbor multiple DNA alterations that can now be readily identified using newer technologies. Although this approach has yielded an unprecedented amount of information regarding the genetic makeup of an individual’s tumor, it has also created many new areas of uncertainty and unmet needs. In this section, we shall review various DNA sequencing technologies and testing platforms, and how they can potentially be used for clinical utility and patient benefit.

Germline Versus Somatic DNA Alterations in Cancer
To understand the nature of DNA sequencing of tumors, one must first understand the differences between DNA alterations that are heritable, which can lead to an increased predisposition toward cancer formation, compared with DNA alterations that are present only in cancer cells. Inside most cells of the body, there are generally two copies (diploid) of the human genome. Gametes (ova and sperm) contain a haploid genome (one copy), thus allowing for the zygote to inherit half of its DNA from each parent. DNA obtained from normal cells is often referred to as constitutional or “germline,” as it is derived from parental ova and sperm, also known as germ cells. Therefore, germline DNA is heritable and can be passed down to progeny. If there is a mutation present in one haploid genome (e.g., BRCA1 mutation), then it logically follows that there is a 50/50 chance of each offspring inheriting the mutant versus wild-type copy of the gene.

Even in cases of heritable mutations (e.g., BRCA1), cancer formation still requires additional genetic alterations or “hits” that will occur only in the cancer cells. Such alterations are termed “somatic” and it is thought that generally three or more alterations are minimally needed for a cell to transform into a cancer, though progression and metastatic lesions will generally acquire additional DNA alterations. Regardless, in clinical oncology both germline testing using normal cells (e.g., saliva/cheek swabs, peripheral lymphocytes from blood) and tumor testing are being performed routinely, but only a limited number of tests incorporate both germline and tumor testing. As described below, this can influence the interpretation of DNA test results. Thus, physicians and health care providers should be aware of these caveats when ordering and receiving these genetic tests.
DNA Detection Technologies

Although several research and commercial tests are now available for detecting mutations and other DNA alterations, most tumor testing is currently performed with NGS. Although “first-generation” Sanger sequencing was the gold standard for years in both research and clinical laboratory testing, NGS has largely supplanted Sanger sequencing for cancer research and companion diagnostic use in clinical oncology.

NGS involves shearing of DNA into small (200 base pairs) fragments that are then used to create DNA libraries. Each library generally represents one patient sample, either tumor tissue or normal DNA, and contains millions to billions of individual DNA fragments. Each of these DNA fragments is then sequenced individually, but also simultaneously, such that this massively and in parallel approach yields terabytes or more of DNA sequencing data. Repetitive or redundant sequencing is generally needed to ensure that each nucleotide of a given DNA position is sequenced enough times to distinguish true mutations from NGS artifacts that can occur during the creation of libraries and the sequencing process itself. The advent of modern computers and electronic public databases then allow for each sequenced DNA molecule to be aligned against a reference genome to determine the presence or absence of mutations relative to the reference sequence.

Because reference genomes are derived from a variety of pooled individuals, it is not always possible to distinguish a mutation from a normal variant that could exist within the population. This is true for both germline and tumor-only sequencing where the term “variant of unknown significance” is often applied. As such, germline sequencing and filtering is becoming more commonplace for sequencing in human cancers, are so common that germline controls to verify that they are somatic were not needed. Examples of such mutations are abundant, but include E545K and H1047R mutations in the PIK3CA gene, and G12 and G13 codon mutations in KRAS. With the advent of NGS, whole-genome sequencing became a reality, though the cost and turnaround time precluded its initial widespread use with the original NGS platforms. As such, various methods were developed that allowed for selecting and sequencing of only certain hotspot mutations using NGS, greatly facilitating tumor sequencing in terms of cost and time. With time and further maturation of NGS technology, this was expanded to include multiple cancer genes, some of which capture the whole gene of interest, whereas for other genes only hotspot regions of the gene were included in the test. Therefore, care providers should be wary of potential false negative results in that the sensitivity of a test for a given gene mutation is predicated on which regions of the gene are being queried. Moreover, distinct NGS platforms and differences in variant calling may affect concordance between commercial NGS tests. As such, there has been increased interest in the use of gold standards for internal references across institutions and the varied platforms used for tumor NGS testing.

As NGS technology and computing power have steadily evolved, the ability to sequence greater amounts of DNA with faster throughput at lower cost has made whole-exome sequencing and now even whole-genome sequencing a reality. Most whole-exome sequencing platforms incorporate all coding regions of the human genome and some noncoding regulatory regions such as the hTERT promoter region that contains a mutational hot spot. Given the roughly 50 million and 6 billion base pairs of DNA in a whole exome and whole genome, respectively, identifying true mutations/alterations from normal variants becomes almost untenable without germline filtering when performing whole-exome

Hotspot Mutations, Gene Panels, Whole-Exome and Whole-Genome Sequencing

The need for the aforementioned germline filtering has arisen only recently as greater amounts of tumor DNA sequencing can be performed in a relatively cost- and time-efficient manner. Traditionally with Sanger sequencing, “hotspot” mutations, defined as mutations occurring at high frequency in human cancers, are so common that germline controls to verify that they are somatic were not needed. Examples of such mutations are abundant, but include E545K and H1047R mutations in the PIK3CA gene, and G12 and G13 codon mutations in KRAS. With the advent of NGS, whole-genome sequencing became a reality, though the cost and turnaround time precluded its initial widespread use with the original NGS platforms. As such, various methods were developed that allowed for selecting and sequencing of only certain hotspot mutations using NGS, greatly facilitating tumor sequencing in terms of cost and time. With time and further maturation of NGS technology, this was expanded to include multiple cancer genes, some of which capture the whole gene of interest, whereas for other genes only hotspot regions of the gene were included in the test. Therefore, care providers should be wary of potential false negative results in that the sensitivity of a test for a given gene mutation is predicated on which regions of the gene are being queried. Moreover, distinct NGS platforms and differences in variant calling may affect concordance between commercial NGS tests. As such, there has been increased interest in the use of gold standards for internal references across institutions and the varied platforms used for tumor NGS testing.

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### PRACTICAL APPLICATIONS

- NGS platforms are FDA-approved to screen for genetic abnormalities in cancer.
- NGS results can vary based on sample input, the design of the platform, and the bioinformatics analysis.
- Molecular tumor boards may provide valuable guidance on interpreting and applying test results to patient care.
- Many treatment opportunities are available based on NGS testing through clinical trials.
- Off-label use of targeted therapies alone or in combination may not be covered by insurance and may be toxic.
Cell-Free DNA and Liquid Biopsies

The use of NGS has also brought forth the concept of a liquid biopsy for cancer diagnostic testing. Liquid biopsies originally implied testing for the presence of circulating tumor cells, but more recently, this term has been used to describe assaying for circulating cell-free DNA (cfDNA; reviewed in7). It is well-known that all cells, cancerous and normal, shed DNA into the circulation. This cfDNA can be isolated and analyzed by NGS for a variety of purposes including identifying circulating tumor DNA. Many studies have now been published showing the ability to detect cfDNA using various substrates such as plasma, serum, urine, saliva, and others. NGS along with its predecessor digital polymerase chain reaction8 and other technologies have now become routine for detecting somatic alterations in cfDNA. There is now an FDA-approved liquid biopsy test for patients with lung cancer to determine eligibility for mutant EGFR–targeted therapies.9 Additionally, cfDNA is also being studied as a marker for residual cancer burden, response to therapies, and prognosis.10 If successful, these studies have potential to change practice, allowing for a true precision oncology approach by determining whether therapies are effective in real time and/or monitoring for cfDNA mutations that are markers of resistant or sensitivity to a targeted therapy.

INTERPRETATION OF RESULTS

The Role of a Community-based Molecular Tumor Board

The results from NGS testing can be very difficult to interpret. Technical differences and unique variant classification strategies used by available commercial tests can further complicate interpretation of results. There may or may not be subtraction of germline variants. Sometimes an unrelated mutation may masquerade as an oncogenic driver.11 These complexities have led to difficulties in understanding the results of somatic tumor testing, prioritizing variants identified, identifying appropriate targeted therapy options, and communicating the findings to patients. These difficulties have led many academic institutions to establish molecular tumor boards (MTB).12,13

Many smaller community-based oncology programs do not have the multidisciplinary personnel or experience to support a MTB. Oncology precision medicine (OPM) options for patients in those programs are referral to an academic center that has an OPM/MTB program, partnering with an academic center to create a virtual MTB or targeted treatment recommendations based primarily on the somatic tumor testing report. This latter approach is subject to many of the difficulties described above. These include variability in the understanding of somatic tumor testing results and technical factors among oncology providers, lack of awareness of variant-based clinical trials, lack of awareness of preclinical and clinical data regarding preliminary results of proposed targeted therapy, and not recognizing potential germline variants. It is not practical for all patients who are potential candidates for OPM therapy to be referred to an academic center that has an OPM/MTB. It is possible for larger community-based oncology programs to develop an OPM program with an MTB comprised of clinical oncology personnel typically found in a large community-based program. The Aurora Health Care OPM program (AOPM) is an example of an OPM/MTB in a community-based oncology program.14

The AOPM MTB is comprised of three general medical oncologists who have dedicated a portion of their practice to OPM. There is a dedicated pharmacist who assists in the research of potential targeted therapy options, classification and communication of MTB recommendations, and obtaining of authorization for off-label targeted drug use. A research coordinator helps identify variant-based clinical trial options both within and outside Aurora Health Care. An OCN certified nurse functions as the program coordinator and helps arrange biopsies, authorization for comprehensive somatic tumor testing, and helps manage the clinic. A genetic counselor reviews all reported pathogenic/likely pathogenic variants as well as variants of uncertain significance. Variant allele frequency results are obtained from the vendor if not included within the report. The results of the vendor-specific algorithm for classification of somatic versus germline variants are reviewed. A family pedigree is reviewed. A recommendation for or against additional genetic counseling/germline genetic testing is then given. A pathologist with a molecular pathology background reviews pathology results and assists with understanding the molecular biology of an identified variant or variants. All comprehensive somatic tumor testing is arranged through the AOPM clinic. This helps ensure that the appropriate test is being performed on an appropriate patient at the appropriate time. All tests are then reviewed at the AOPM MTB, and results are communicated to the primary oncologist. If desired by the patient or primary oncologist, patient evaluation can occur in-person at the AOPM clinic. Once a recommendation is made, the patient is referred back to the primary oncologist for ongoing care.

The treatment goals of the AOPM program are first to identify standard-of-care treatment options, including FDA-approved targeted therapy for a patient’s particular tumor type and FDA-approved tumor-agnostic immunotherapy treatment options. Most often, these treatments have already been exhausted by the time a patient is evaluated at the AOPM clinic. When there are no standard-of-care targeted therapy options, the priority is for variant-based clinical trial options, targeted treatment approaches supported by well-powered studies, or consensus statements or FDA-approved targeted treatment approaches in another tumor type. Finally, options for targeted treatment approaches based on preclinical data or case reports are
considered. In addition, the comprehensive evaluation of the somatic tumor test result by our genomic medicine group minimizes the risk of missing a germline mutation that could have significant impact on the treatment of the patient and case identification within the patient’s family.

The administrative goals of the AOPM program are to obtain the most value OPM has to offer. There are some that question the value of precision medicine–based targeted therapy approaches in patients who have exhausted standard-of-care treatment. By centralizing the ordering of comprehensive somatic tumor testing, the AOPM maximizes the likelihood of obtaining the most appropriate tumor sample and somatic tumor test. In addition, it affords the opportunity to identify patients who are not appropriate for OPM evaluation because they are near end-of-life or there are standard-of-care treatment options that are more appropriate.

Recommendations from the AOPM MTB are summarized in a formal template document that is sent to the referring primary oncologist. In addition, the primary oncologist is encouraged to participate in the MTB by video conferencing when their patient is presented. For patients evaluated in person at the AOPM clinic, these recommendations are also communicated to the patient. The format of the recommendations is a modification of published guidelines. Level A recommendations are FDA-approved therapies. Level B recommendations are based on well-powered studies with support from expert panel guidelines. Level C recommendations are based on FDA-approved targeted therapy in another tumor type or variant-specific investigational trials. Level D recommendations are based on preclinical data or case reports. There is also a review of PD-L1 immunohistochemical test results, microsatellite instability testing, and mutational burden that may impact the role of immunotherapy. Lastly, if indicated, recommendations for genetic counseling and germline genetic testing are given.

TREATMENT SELECTION BASED ON NGS Identification of Biomarkers for FDA-Approved Therapy

The results of NGS testing may identify a mutation that predicts benefit with a specific treatment in accordance with FDA-approved product labeling. Various assays may fail to detect an actionable mutation due to low tumor percentage or other technical issues. Accordingly, testing with NGS may identify the presence of a sensitizing mutation that was previously missed. In other cases, previous testing may not have been performed or may not have included assessment of FDA-approved indications. For example, the FDA recently granted accelerated approval of pembrolizumab for the treatment of any adult or pediatric solid tumor that is unresectable or metastatic with microsatellite instability–high (MSI-H) or mismatch repair deficiency. Prior testing, if performed, may not have included assessment of microsatellite instability–high or mismatch repair deficiency. Additionally, the temporal evolution of a tumor may benefit from repeat assessment. For example, in some patients with EGFR-mutant non–small cell lung cancer repeat testing at the time of tumor progression may detect the EGFR T790M resistance mutation that may be treated with the FDA-approved therapy osimertinib.

Clinical Trial Selection

The development of NGS and targeted therapies has dramatically changed the design, scope, endpoints, and assumptions of clinical trials in oncology. Many clinical trials now incorporate NGS testing or consider the results of external NGS testing for patient selection. These clinical trials range in scope from phase I, single-agent trials to large multi-institutional platform studies that test many agents based on molecular profiles in a histology-agnostic fashion. Although it is beyond the scope of this review to cover all of the potential clinical trial opportunities for patients based on the results NGS testing, we strongly encourage that the results of NGS testing, if performed, be used to identify clinical trial opportunities when FDA-approved therapies are not available.

There are many examples of clinical trials that assign treatments based on the molecular profile of a tumor in a histology-agnostic fashion. In other words, regardless of the tumor type, as long as it is one of the many allowed, patients may be considered for treatment with a targeted agent if the right molecular profile is identified, so called “basket trials.” Examples of molecular-based studies include ASCO’s Target Agent and Profiling Utilization Registry Study (TAPUR; NCT02693535), the National Cancer Institute’s Molecular Analysis for Therapy Choice (NCT02465060) and Molecular Profiling-Based Targeted Therapy (MPACT; NCT01827384), and Genentech’s “My Pathway” (NCT02091141). Other clinical trial opportunities are specific to a tumor type or subtype, but select patients for treatment based on common molecular profiles for that malignancy, so called “umbrella trials.” Examples of these tumor-specific trials with multiple treatment arms include BEAT AML (NCT02927106) for patients with acute myeloid leukemia, ALCHEMIST (NCT0219438) for patients with resected non–small cell lung cancer, and Lung-MAP (NCT02154490) for patients with metastatic squamous non–small cell lung cancer who are being considered for second-line therapy. Many of these clinical trials are dynamic, with an expanding number of potential treatments and eligibility modifications that allow an increasing number of screening assays. Accordingly, we have not covered the methods of screening and potential treatment options in detail here, but we recommend consideration of these clinical trials or others like them given their broad coverage of tumor types and potential therapeutic opportunities.

In other applications of NGS, early-stage cancer therapeutics programs may use the results of such testing to guide recommendations for phase I clinical trials of targeted therapies. Some of these clinical trials may require external validation of the molecular abnormality in question prior to treatment, such as MET exon 14 skipping mutations for treatment with the oral cMET inhibitor capmatinib (INC280)
in patients with non–small cell lung cancer (NCT02414139). Other clinical trials allow validation of the molecular abnormality after enrollment such as the study of entrectinib for patients with NTRK1/2/3, ROS1, or ALK rearrangements (NCT02568267). Regardless, there are early reports that this approach is increasingly being used at academic centers to facilitate genotype-based assignment to clinical trials.29,30

Although NGS can identify many mutations, some biomarker-driven clinical trials are based on the expression of a biomarker detected with a proprietary assay. Some examples of these basket studies include testing for mesothelin or DLL3 in solid tumors for selection of patients to receive the antimesothelin antibody-drug conjugate anetumab rantasine (NCT03102320) or the anti-DLL3 antibody-drug conjugate rovalpituzumab tesirine (NCT02709889), respectively. For basket studies like these, oncologists may screen all of their patients who are seeking clinical trial opportunities after failure of standard-of-care treatments. They may also use pretest probabilities based on published data of expression patterns to decide whom to screen for various studies, or they may use NGS transcriptome analysis to guide screening decisions. These basket trials allow exploration of clinical activity across a broader range of tumor types than for which an investigational agent may have initially been designed.

**Expanded Access**

Expanded access (or compassionate use) provides patients with life-threatening diseases without therapeutic alternatives access to investigational drugs. Expanded access to investigational products is regulated by different agencies with authority in their respective countries. Sometimes definitions used by one agency are not used by another, and these varying uses have led to confusion.21 Herein, we focus on the expanded access program within the United States as regulated by the FDA, and we refer readers to other reviews22 and policies such as the European Medicines Agency statements on the compassionate use program and named patient program if relevant to their needs.23

Following a successful clinical trial, pharmaceutical companies may design expanded access clinical trials to provide access to an effective therapy during regulatory review. These clinical trials may provide a treatment targeted to the molecular profile of patients’ tumors and are very reasonable to consider when available. On the other hand, the majority of expanded access requests to the FDA are for the treatment of individual patients. The Center of Drug Evaluation and Research at the FDA receives over 1,000 applications a year for expanded access, and the majority of these are for oncologic or hematologic products.24 Most of these single-patient requests are approved and seldom result in drug development delays due to adverse events.24 Despite efforts to minimize the administrative burden of expanded access requests, there are many steps a physician must take to sponsor expanded access for a single patient. The time commitment required for physicians to sponsor single-patient expanded access simply limits the number of requests that a physician can make. The FDA requires that many conditions be met to approve expanded access for patients (Sidebar 1). Situations where physicians might want to consider requesting expanded access for a patient include when there is a strong biologic rationale to suggest benefit from an investigational agent or when a patient is not a candidate for a clinical trial with the investigational agent because of overly restrictive eligibility criteria25 that would not likely worsen the patient’s risk or safety profile of the agent (e.g., alkaline phosphatase is higher than permitted due to bone metastases) or reduce the potential efficacy of the investigational agent (e.g., gastrointestinal disease that limits absorption of oral agent). This approach can sometimes be very successful,26 but little is known about the overall efficacy of single-patient expanded access.

**Off-Label Prescribing**

Off-label use refers to any prescribed use that is not consistent with the FDA-approval for an agent. There are many types of off-label use including the prescription of an agent

### SIDEBAR 1. U.S. Food and Drug Administration Requirements for Expanded Access

- The patient and a licensed physician are both willing to participate.
- The patient’s physician determines that there is no comparable or satisfactory therapy available to diagnose, monitor, or treat the patient’s disease or condition.
- That the probable risk to the person from the investigational product is not greater than the probable risk from the disease or condition.
- FDA determines that there is sufficient evidence of the safety and effectiveness of the investigational product to support its use in the particular circumstance.
- FDA determines that providing the investigational product will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval.
- The sponsor (generally the company developing the investigational product for commercial use) or the clinical investigator (or the patient’s physician in the case of a single-patient expanded access request) submits a clinical protocol (a document that describes the treatment plan for the patient) that is consistent with FDA’s statute and applicable regulations for INDs or IDEs, describing the use of the investigational product.
- The patient is unable to obtain the investigational drug under another IND or to participate in a clinical trial.

Abbreviations: FDA, U.S. Food and Drug Administration; IND, investigational new drug; IDE, investigational device exemption application.
for a different indication (e.g., breast cancer instead of lung cancer; patients with earlier stages of disease), route of administration (e.g., subcutaneous rather than intravenous), or dosing (prescribed dose not specified in the label or prescribed in nonapproved combinations) than what is on the label. Off-label use of cancer therapeutics is not always done without evidence or support of professional guidelines. For example, in a randomized, controlled phase III clinical trial, bevacizumab was found to improve survival when added to cisplatin and pemetrexed compared with the combination of cisplatin and pemetrexed in patients with mesothelioma. The National Comprehensive Cancer Network guidelines now recommend bevacizumab in this setting, even though it does not have FDA approval and is unlikely to receive such. Other examples of off-label use occur after the successful completion of a clinical trial before regulatory FDA approval. We would caution that successful clinical trials do not always lead to FDA approvals given issues that may arise during regulatory review such as the lack of confirmation of responses. Although these off-label uses are reasonable, extensive use of off-label cancer treatments without proven safety or efficacy is a public concern. It seems that off-label use of cancer treatments supported by evidence or not, is rampant in oncology. Although one review of intravenous chemotherapy use published in 2013 reported that 70% of use was on-label and met FDA-approved indications, others have suggested that off-label use is as high as 75%. NGS and other techniques have revolutionized our understanding of tumor biology, molecular heterogeneity, and clonal evolution. These techniques have been applied to the design of clinical trials and institutional practices using levels of evidence ranging from preclinical data with cell lines to various phases of clinical trials to assign patients to targeted therapies. As our understanding of tumor biology is continually refined, many investigators now suggest that the redundancy of signaling pathways and resistance mechanisms that develop to targeted therapy favor combinations of therapeutics for greater clinical efficacy. Although we fully support the development and investigations of therapeutic combination strategies based on molecular insights gained from profiling with NGS or other techniques, we caution against the use of unproven treatment combinations outside of clinical trials given their potential toxicity. For example, the combination of vemurafenib and ipilimumab for the treatment of melanoma had a high rate of unanticipated hepatotoxicity, and the combination of osimertinib and durvalumab for the treatment of EGFR-mutant NSCLC had higher rates of pulmonary toxicity than predicted with either agent alone. Along these lines, and given the frequent use of off-label targeted therapies, others have argued that the safety, efficacy, and cost of off-label medications or combinations must be considered when deciding to prescribe such. Under this proposed framework, if the safety of a combination has not been established or a trial suggests that a combination is not effective, insurers should not necessarily be responsible for covering the costs of such off-label use.

**Registries**

As per above, we strongly recommend that FDA-approved treatments, clinical trials, or expanded access be pursued for patients in the appropriate clinical scenarios. When other means of treatments are pursued based on NGS profiling, it may inform future development to provide clinical annotations to the detected molecular profiles in one of many available prospective registries. Most of these registries have a similar goal of advancing OPM by tracking patient outcomes and responses to treatments in relation to the profiles of their tumors. Examples of these include the American Association for Cancer Research’s Genomics Evidence Neoplasia Information Exchange (GENIE), CureOne, the Multiple Myeloma Research Foundation’s COMPPASS, the Bladder Cancer Advocacy Network’s Bladder Cancer Genomic Consortium, and the Pancreatic Cancer Action Network’s Know Your Tumor.

**Expanded Access, Right-to-Try, and Off-Label Controversies**

Formal product approval by the FDA requires review of the safety and efficacy of an investigational treatment. The time this takes may delay access following the completion of a successful clinical trial, but is necessary to ensure that patients are not exposed to ineffective or harmful treatments. As per above, expanded access is allowed when situations meet certain criteria (Sidebar 1) and helps reconcile access to potentially effective therapies with protection of the public from harmful agents by full review. The availability of expanded access and off-label use may unfortunately deter or compete for enrollment into clinical trials that are necessary to gain regulatory approval of an agent. Expanded access may also compete with the limited supply of an investigational agent needed for confirmatory clinical trials. Manufacturers are not required to provide investigational agents for expanded access and are allowed to charge for direct costs related to the manufacturing, shipping, and monitoring of the agent. As others have mentioned, the best pathway to make investigational products available to most patients in need is to demonstrate their safety and efficacy for full and prompt FDA approval. Thus, it is only in limited circumstances that we recommend expanded access be pursued as per above.

“Right-to-Try” legislation has been enacted in many states but not at a federal level. This legislation is largely modeled after a proposal from the Goldwater Foundation in Arizona that was designed to subvert and bypass the FDA. Right-to-try legislation varies by state but typically allows patients to access investigational agents that have successfully passed phase I clinical trials, are the subject of FDA clinical trials, and are not yet available to the public, as is the case in Minnesota. Similar to FDA expanded access, manufacturers are not mandated to make these investigational agents available under “Right-to-Try” laws. Similarly, physicians cannot be forced to prescribe these medications and may have protections at the state level from prescribing these agents. Many physicians believe that these “Right-to-Try”
laws will have negative, unintended consequences for patients through the removal of safeguards, jeopardization of insurance coverage, and circumvention of the government’s responsibility to monitor investigational products. Professional societies including ASCO have opposed these laws. The antiregulatory sentiment directed toward the FDA is often unfounded given that the FDA approves more than 99% of expanded access requests, typically within 1 day of receipt, and has streamlined its approval process with breakthrough designations and accelerated approvals. Given that state approvals of “Right-to-Try” laws conflict with federal law, it has been recommended that physicians continue to comply with federal prescribing laws.

False Optimism

Although there are examples of tremendous successes with OPM, NGS screening may provide false optimism to some patients with poor performance status who are unlikely to receive additional lines of therapy. In these situations, referral to palliative care, if not made already, and consideration of hospice may be most appropriate.

CONCLUSION

Molecular profiling has revolutionized oncology. Many targeted therapies and, more recently, immunotherapies have been approved by the FDA with companion diagnostic tests. NGS platforms are now approved to screen for many of these abnormalities. In some malignancies like non–small cell lung cancer, it might be cheaper to screen for all of the recommended biomarkers with an NGS-based cancer panel rather than testing for each biomarker individually. In other uses, NGS may be used to guide treatment assignment in clinical trials or guide clinical trial recommendations. Given the developing interest in combination therapies that are tailored to the unique molecular profiles of individual tumors, others have noted the irony that “while cancer treatments themselves are becoming more precisely targeted, the evidence upon what clinical decisions will be made is becoming much less precise.” Along these lines, we strongly encourage that use of NGS in clinical use be used to guide selection of FDA-approved therapies or to direct patients to clinical trial opportunities to facilitate the most expeditious approval of investigational agents.

References


No Decision Is Final: Career Planning and Career Transitions

Brian Boulmay, MD, Tatiana Prowell, MD, Marcelo Blaya, MD, and Maria Catherine Pietanza, MD

OVERVIEW

Several factors play a role in job selection after completion of a hematology/oncology training program, such as a fellows’ overall career goals, expected income potential, and limitations imposed by visa status, among many others. Training programs play an integral role in mentoring trainees in career selection. For many, the first job is often not career-long. In addition to considerations for a fellow considering a first job out of fellowship, physicians will consider a change because of dissatisfaction at one’s current position, desire for advancement opportunities, or a desire to work in a different sector. Other factors include non-occupational issues such as career opportunities for a spouse or desire for a different geographic location. Frequent employment changes are common with crossover between academia, clinical practice, industry, or government service. Possessing the skills needed to recognize one’s strengths, weaknesses, and goal prioritization can allow for more optimal job selection should a career transition into a different discipline occur. Recognizing opportunities that present themselves and potentially taking advantage of them can lead to professional and personal growth.

There are many factors that a fellow and program director should consider when discussing career paths most suitable for a trainee. Fundamentally, the main question should be what do we anticipate will be the most appropriate for the fellow for the long term? Trainees will consider best matches for personality type, income goals, and geographic preferences. Often, not every factor the fellow desires can be optimally matched, and some compromises will likely be made in final job selection. Additionally, limitations are often present for those with certain training visas. Laying the foundation for future employment should begin as early as the first year of fellowship. This will be especially important if a fellow is interested in pursuing a successful, immediately productive academic career.

PREPARING TRAINEES FOR THE REAL WORLD: EXPLORING OPTIONS WITHIN ONCOLOGY

Traditional academic-based fellowships have focused on preparing trainees for success in three general areas: competency in clinical practice and demonstration of academic productivity and medical knowledge, primarily by ensuring board passage. These components are the basis upon which the core competencies of the Accreditation Council for Graduate Medical Education expectations are built. Although the requirements for graduate medical education for hematology/oncology programs emphasize the training of a successful fellow for competent clinical practice, the program directors’ specific responsibilities in preparing a trainee for a postfellowship career are not emphasized. Even though the primary role of the program director in an academic program is as a teacher, mentoring plays a large part of fellow interaction, especially as it relates to career selection. For example, one study showed that 90% of fellows interested in academic practice viewed mentorship as an important factor when selecting a career. Fellows influenced by positive role modeling are more likely to follow the mentor’s career path. Trainees are also strongly influenced by their perception of the mentor’s own job satisfaction and lifestyle to help inform their job choice.

Of the 146 hematology/oncology programs currently accredited in the United States, the majority are associated with a medical school. It is a fair assumption that many of the directors of these programs have a focus on training academic clinicians. However, based on the most recent ASCO survey data, only 39% of hematology/oncology fellowship graduates are in an academic practice. The remaining 56% have a clinical practice, with a smaller percentage going into government service (3%) or industry occupations (1%). Current workforce data from the American Medical Association for 2013 to 2014, show that 61% of oncolists work in a clinical group practice, with a small percentage working directly for a medical school setting (2.5%).

The milieu in which a fellow trains may influence career choice. For example, at NCI/NCCN-designated cancer centers in 2008, 59% of graduating fellows entered academic practice, 38% entered nonacademic practice, and 3% took a position in the pharmaceutical industry. The differences in career destination for fellows from these more research-based...
programs compared with the total graduating fellow cohort are difficult to establish. Data from the ASCO In-Training Examination (ITE) post-test questionnaire are instructive. Third-year fellows taking the ITE were asked to indicate what their employment expectations were upon graduation. In 2014, based on 420 responses, 48.1% were planning to work in academic practice and 46% in community/private practice. Survey data from 2017 (513 respondents) showed an even higher percentage planning to enter university-based practice upon graduation (57%; unpublished data from ASCO Center for Research and Analytics, January 29, 2018). Although an NCI/NCCN-designated cancer center may more favorably foster an environment for training academicians, it appears that there is a fair alignment of career destinations independent of training site as the ASCO ITE reflects fellows from both NCCN/NCI-designated and nondesignated centers.

Income potential at graduation is a critical consideration for new employment. Nationally, the mean indebtedness of medical school graduates in 2014 was $176,384, with 10% of graduates having educational debt of more than $300,000.6 Salary information can be opaque, but national self-reported data are increasingly available on physician networking sites. The mean salary of a community oncologist is dependent on region, but is estimated to be approximately $330,000, with academics reported to make 13% less.7,8 How much debt influences fellows’ individual career choice is also unclear. Data would suggest that income potential does influence career choice at the medical school and fellowship levels.9,10 With a trend toward private oncologists being hospital employed or hospital-based, the financial risks associated with private practice has decreased, along with income potential. The compensation arrangement of many academic practices has also evolved to match more closely the private models’ RVU-based compensation and incentive structure. Over time, pay differential between private practice and academics may become less of a factor in a fellow’s career choice.

Forty percent of hematologist/oncologists are international medical graduates. As a result of a fellow’s training visa, their first choice of employment may not be feasible. For example, fellows holding a J1 visa who wish to continue working in the United States upon graduation must apply for a waiver allowing them to remain in the United States. The so-called Conrad-30 program is the most common mechanism for doing so and was designed primarily to address a shortage of physicians in medically underserved areas. The waiver allows the visa holder to remain in the United States for a 3-year term, after which he or she can apply for permanent resident status. Thirty waivers are provided to each state every year, with states giving highest preference to primary care specialties such as internal medicine or pediatrics. Consequently, large population states, such as California, frequently fill their waiver slots with primary care physicians, although some smaller states do not fill all of their slots. In addition, many employers choose not to hire candidates with a Conrad-30 waiver because of the relatively prolonged and costly process associated with the waiver, further limiting employment opportunities. As a result of the competitive nature of the waiver program, fellows are advised to secure employment as early in their third year of fellowship as possible to ensure a Conrad-30 waiver can be obtained.

**SEEKING NEW OPPORTUNITIES AND WHAT TO LOOK FOR**

Any efficient job search begins with asking why a new job is being contemplated at all. There are a few broad reasons that lead people to consider changing jobs: unhappiness at one’s current job, desire for advancement opportunities that do not exist in the current organization, interest in working in a completely different sector or field, and nonoccupational issues such as career opportunities for a spouse or desire to live closer to family. These are not mutually exclusive, and there are often multiple reasons for seeking a change. Nonetheless, it is impossible to generate a specific wish list of desirable aspects for a new position without pausing to reflect on the positive and negative attributes of one’s current job and what is prompting a job search in the first place. This process facilitates asking whether one’s current institution is willing and able to make changes that would address the sources of dissatisfaction. It is far less expensive in terms of cost, morale, and productivity to retain existing talent than to recruit and hire new employees. Therefore, although employers may not spontaneously offer certain perks such as more protected time for research, a flexible work schedule, or an additional administrative assistant, they may nonetheless be willing to consider changes if approached by someone they are motivated to retain.11

In some cases, the changes needed to achieve job satisfaction will not be feasible and a move to a new institution or company will be essential. The first step is to critically assess one’s own personality, strengths, and weaknesses to identify opportunities that will be the best fit for a given individual. This can be done formally via any number of online
assessment tools such as Clifton Strengths, which characterizes an individual’s unique mix of talents, or DiSC, which identifies patterns of behavior in four domains (dominance, influence, steadiness, and conscientiousness). Alternatively, an individual may be able to informally characterize his or her own personality, strengths, and weaknesses using a simple process of honest self-reflection and insight from trusted relatives, friends, or colleagues.

A good career opportunity will exploit an individual’s personal strengths and limit the negative impact of personal weaknesses. For example, a physician who values routine and tolerates unpredictability poorly may experience rapid burnout in an academic role that consists of an erratic schedule of inpatient attending, grant writing, research projects, and professional travel, but be a very valuable and satisfied partner in a private practice. Indeed, the best career opportunities for an individual may even render personal “weaknesses” advantageous. A physician who is easily bored and impatient may be a problematic colleague in private practice or basic science research, but extremely successful and happy working in a start-up biotechnology company. A thorough and honest self-assessment is the foundation of every good job match.

After reflection, it is worth asking which aspects of one’s current job bring joy. A simple way to approach this is by keeping a daily journal for a period of weeks to months in which one notes particularly satisfying workdays and how time was spent that day. This process of mindful journaling will help answer one of the most critical questions when considering a new job: what do you actually want to be doing all day? Do you find days spent working alone isolating, or do such days enable you to be focused and at your most productive? Do you leave a day-long scientific meeting with colleagues energized by the exchange of ideas and potential for new collaboration, or do you consider meetings to be an inefficient use of time? Do you gravitate toward work with more immediate impact, such as direct patient care, or would you prefer conducting clinical research that may have far-reaching impact but requires tolerance for delayed gratification? These sorts of questions will help to identify whether the most appropriate move is a new role within the same organization, a change of employer, a change of sector, or something else, and journaling is a concrete way to identify personal patterns in what activities bring joy. For example, if the best days include staffing the fellows’ clinic or precepting medical students once a month, one might conclude that an academic position with greater educational responsibilities, potentially even at the same institution, would be ideal. If the most satisfying days involve attending scientific conferences or participating in a multidisciplinary tumor board, one might conclude that generous support for continuing medical education and frequent opportunities for exchange of ideas with peers are must-have features for a future position, regardless of the chosen sector. If workdays during which one can manage to attend a child’s school event or make it home in time for dinner with the family are perceived most positively, an applicant should prioritize positions or sectors with greater inherent flexibility, emphasis on work-life balance, or openness to job sharing, part-time, and telework arrangements. As mentioned previously, there is no one-size-fits-all dream career opportunity.

Steve Jobs, the cofounder of Apple, famously said, “I have looked in the mirror every morning and asked myself: ‘If today were the last day of my life, would I want to do what I am about to do today?’ And whenever the answer has been ‘no’ for too many days in a row, I know I must change something.” It is also critical to document days in which one felt unsatisfied at work and what tasks occupied those days. If the motivation for seeking a new position is frustration with a current job, one might begin by asking whether the sources of dissatisfaction could be adequately addressed without changing jobs and if a new job can remedy the issue. For example, if an oncologist in a private practice enjoys clinical medicine, is satisfied with her patient volume, and has great camaraderie with her partners, but dislikes the amount of time spent documenting in the electronic medical record, would it be possible to hire a scribe to help with this task in her current practice? If not, in her job search, she should prioritize practices that have embraced the use of scribes or midlevel providers to assist with documentation. Simply moving to another private practice without these features is unlikely to address the true source of her dissatisfaction given the national trend toward increasing time spent on documentation in the electronic medical record. Likewise, oncologists in academic medicine who enjoy conducting translational research but have insufficient time to devote to it because of clinical demands in their current position might be happy in the same institution if given more protected time for research. If this is not possible, a new research position in industry or government with fewer or no clinical responsibilities may be a perfect fit.

Although there is no one ideal job for every candidate, there are nonetheless some universal features of good career opportunities. The first is a commitment to employee well-being. In the simplest terms, it is an institution-wide recognition that employees have a life outside of work, and that this is not an inconvenience to be managed, but rather vital to the long-term health of the individual and the institution. This may manifest in a variety of ways, such as affordable onsite childcare, free fitness facilities, potential for telework, or mindfulness meditation classes during the workday that employees are encouraged to attend. If the existing employees have time for hobbies or their families and discuss them without apology, this is a good sign. The second is the potential for continued professional development and growth within the organization. Although it is certainly possible to ascend the career ladder by moving to a new company or institution every 2 to 3 years, the need for recurrent moves may be undesirable for personal or family reasons, such as concerns for geographic stability or a spouse’s career. An ideal job opportunity will therefore include both a general blueprint and some anticipated openings for career advancement within the organization. Another aspect is a clear sense that an organization’s
employees have personal agency. Institutions that actively seek employee feedback and demonstrate willingness and ability to evolve to address the concerns of their employees will result in a happier work environment. Ideal positions will also include adequate administrative and ancillary support. A common complaint across many sectors is that highly educated and trained individuals waste time doing tasks that could be performed by someone lacking their professional expertise. The best organizations recognize that physicians and scientists who are able to use their skillset to its full potential will be happier, more loyal, and more productive and will hire sufficient administrative, research, or other assistants to facilitate that. Lastly, a culture of fairness and meritocracy is important. This includes, among other things, transparency with regards to salary and criteria for promotion that seek to address gender, racial, and other societal inequalities.

As a cautionary note, we would remind readers of the phenomenon of hedonic adaptation, also known as the hedonic treadmill. In 1978, Brickman and colleagues published a classic study in which 22 major winners of the Illinois State lottery were interviewed and compared with 29 victims of accidents that had resulted in paraplegia or quadriplegia. This study revealed two important insights. The first is that the ratings of everyday happiness were strikingly similar between the two groups despite what one might consider dramatically different degrees of good fortune: on a scale of 0-5, lottery winners rated their everyday happiness as 3.33 compared with 3.48 for the paralyzed accident victims. The second was that the accident victims derived more happiness from small, relatively mundane pleasures, such as hearing a good joke or eating breakfast, than the lottery winners. Subsequent studies have reported similar findings. Hedonic adaptation therefore refers to the theory that we have a thermostat-like setting for our long-term happiness that returns to a relatively constant range over time despite external circumstances. When contemplating a job change because of “unhappiness” with no specific complaints about one’s current position, particularly when an individual has changed jobs repeatedly because of unhappiness, the idea that the next job may offer a higher salary or more prestigious title and short-term happiness should be weighed against a negligible long-term impact on day to day happiness or career enjoyment. This may lead one to weight relatively underemphasized job features, such as length of time spent commuting or the nature of the surrounding community, more heavily in ranking potential job opportunities.

A personal reflection from an author of this paper (M. C. P.) is instructive regarding the challenges and possibilities inherent in a career transition.

**TRANSITIONING FROM ACADEMIC MEDICINE: REFLECTIONS ON A CAREER MOVE**

Upon completion of my medical oncology fellowship in 2007, the most obvious career choice for me was one in academic medicine. Years of training and observing my mentors and their accomplishments crystallized what I wanted for my professional life: patient practice coupled with the opportunity to participate in clinical research, develop trials, and collaborate with laboratory scientists to study new therapies and better understand cancer biology. The next 8 years of my career unfolded as I had anticipated: my practice grew and my patients—even if afflicted with terminal illness—brought me great satisfaction. I enjoyed teaching and training residents and fellows the oncologic principles in patient care. Simultaneously, I became more deeply engaged in clinical research, strengthening my relationships within and outside my institution, including with the pharmaceutical industry, which yielded early findings. My role as a clinician scientist allowed me to see the positive results of clinical research first-hand, which led to improved outcomes in my patients. Throughout this time, one thing was clear to me as an oncologist, I wanted to improve cancer care, whether through my one-on-one interaction with patients and their families or clinical research.

On a busy clinic day in the summer of 2015, an email reached my inbox alerting me of an open position in industry. Previously, this email would have been ignored: a job in industry was not of interest to me, which was likely a result of inaccurate perceptions and the unfamiliarity with the “other side” of medicine notwithstanding my growing interactions with physicians in the pharmaceutical industry as a principal investigator on clinical trials. As a medical student and trainee, I never had been exposed to an industry job as an option. Yet, I proceeded to read this particular email, which was different from numerous others I had received in the past. Not only did the sender have clear knowledge of my work, she articulated the uniqueness of the position as the Global Director of Scientific Affairs in Oncology. I decided to reply, and soon I embarked on a full interview schedule, meeting multiple scientists and physicians who had either recently entered industry or had been in the pharmaceutical industry for years developing drugs. During my interviews, although I initially held onto to my preconceived notions, I quickly recognized that industry is another venue to be “academic” and offered the opportunity to advance cancer care on a much larger scale. My interviewees impressed me by their obvious commitment to scientific innovation and desire to improve the lives of patients. The global role would enable me to use my first-hand knowledge of patient care and therapeutic approaches in oncology to engage world-renowned physicians and seek additional advice in how the company could conduct research, whereas maintaining the scientific integrity of the program.

I was offered the job, and for weeks, I struggled with the decision to either (a) continue along my current path in my “dream job” or (b) completely change course, where I would leave my comfort zone and my patients, learn new skills, and participate in clinical research in a different way. I sought the advice of many of my former colleagues and mentors who had made the transition; each noted that the resources available in industry, as well as the necessary pace, were unparalleled, which inevitably would lead to contributions.
Notably, I had not interviewed with any other company, nor had I explored other roles in industry, and, as such, I was unfamiliar with other jobs that could be available to me as a medical oncologist. Ultimately, I decided to accept the position as I recognized it as an experience that would only enhance my career as an oncologist.

The first several months were challenging. I sorely missed my patients and noted major differences between my academic career and my global position in the pharmaceutical industry. I have had to adapt to a new corporate culture, which is unlike any hospital bureaucracy I had experienced. The days are constructed differently, with back-to-back meetings, leaving no or few business hours to work on and deliver assignments prior to the hard deadlines. Ideas in academia potentially can materialize into preclinical research and clinical trials if funding and drugs are available, with subsequent publications and presentations to inform colleagues of results (whether positive or negative). In the industry, ideas are not sufficient—projects undergo full review to determine that, in fact, a drug can be brought to patients and markets successfully. In industry, these projects are to be executed in extremely limited timeframes so as to remain competitive. This necessitates working effectively within teams that include statisticians, operations, and commercial and regulatory colleagues, none of whom I had ever worked with previously. In academia, the milestones that must be met for promotion are more tangible, such as publishing in peer-reviewed journals, teaching, and seeing patients. In industry, these milestones can seem less evident.

In spite of the differences between academics and the pharmaceutical industry, there are striking similarities. I have quickly learned that my training led me here. The rigorous hours spent in training prepared me in a way that only a handful of my colleagues also understand, as the days in industry are long. As noted earlier, the skills taught in training are crucial: competency in clinical practice, productivity, and, most importantly, medical knowledge, which is essential as we make decisions in clinical trial design, interpret and integrate data, and disseminate information to others.

Success in industry requires many of the same principles as in academics: a strong clinical background, a comprehensive field of work, an understanding of the fundamentals of research, and an ability to communicate effectively. It is important to have an appreciation of the patient population and the complexity of the disease, as these help determine what the unmet medical needs are and how to develop clinical trials. As oncologists in industry, we must appreciate the intricacies of the approaches to treatment, be knowledgeable of therapies available, and interpret and apply findings from preclinical data and early-phase studies. To conduct meaningful studies, it is critical to understand hypothesis testing and statistics to develop a protocol; to implement the outlined plan whereas maintaining the safety of the population; and to perform an analysis of the findings. Finally, our findings must be communicated to regulatory agencies, investigators, physicians, and patients.

Notably, the roles in industry are vast and include, among others, early discovery, translational medicine, biomarker experts, statisticians, clinical development, clinical operations, regulatory affairs, safety, epidemiology, scientific and medical affairs, and commercial development. Experts in all of these areas must collaborate and work effectively in teams for a company to successfully bring a drug to market. In addition, close collaborations between regulatory agencies and academics are essential for this to occur. Before transitioning to industry, I did not fully appreciate the details necessary to enable a new therapy to reach a patient.

These numerous roles provide physicians with opportunities to change functions and responsibilities within the same organization, which often is favored to retain talent. Within 12 months of being in the role for which I had been recruited, I recognized that I needed to be more directly involved in clinical research at the company and transitioned to a position in development. My mentors equally noted that this is where I would flourish and allowed the move to occur.

I do not know what my future will bring, and, although I still have a lot to learn in my current role, my experience in industry has made me a better oncologist. I better understand the global environment and can more easily communicate with physicians worldwide. I better recognize the regulatory hurdles to drug approval and have a better appreciation of how a drug reaches the patient in clinic. Finally, I continue to pursue my goal of improving cancer care, although now at a global scale, which I would not have the opportunity to do previously.

In training future oncologists, we owe them exposure to industry early in training, which may be accomplished by holding seminars with representatives from pharmaceutical companies. Trainees could use this opportunity to learn how drugs are brought to market. Additionally, elective opportunities could be developed to allow industry physicians to highlight how they impact clinical research. Such activities may offer trainees and young oncologists an improved understanding of the roles available and allow industry to be considered as a career option.

CONCLUSION

Identifying and selecting an employment opportunity upon graduation is an important step in a fellow’s working life. However, for many the first job is likely not going to be a career-long position. Frequent employment changes are common with crossover between academia, clinical practice, industry, or government service. It is unknown what percentage of fellows change jobs within 5 years of graduation, however, anecdotal data would suggest that a decade after completing fellowship, up to 50% of graduates will change jobs at least once (N. Vander Velde, B. Boulmay, and J. Cole, email communication, November 2017). A systemic data collection program determine what factors lead fellows to choose particular jobs or lead to oncologists changing jobs may allow for better matches in the future. For now, in preparing trainees for the “real world,” a foundation should be
established for ensuring adaptability when job changes do occur. For those who have already completed training and now are seeking other opportunities, there is hope that a more ideal fit can be found.

References


The goal of our fellowship education is to train the next generation of hematologists/oncologists to be compassionate, engaged, and knowledgeable physicians with a lifelong desire to learn and thrive in our field. In today’s complex training environment, our fellows are in many different locations, with many different mentors, and engaged in multiple activities. It is necessary to have a straightforward system to measure their progress. The ACGME monitors the training programs with nine annual metrics—program leadership changes, documentation of scholarly activity, program attrition, board pass rate, clinical experience, resident survey, faculty survey, completion of milestone evaluations, and clinical learning environment review. Programs complete one of the metrics, the milestone evaluations for each trainee, twice a year on the ACGME website. The specific reporting milestones vary between specialties, but the overall goal of measuring the skills, knowledge, and behaviors that trainees achieve during training is the same.

ASH and ASCO convened their training program committees and guest experts in 2013 to develop the ASH/ASCO Curricular Milestones. The intent of this activity was to develop a document that would cover all of the activities that are important to our profession and could serve as a tool to monitor progress and develop curriculum. Now, after 4 years of using the ASH/ASCO Curricular Milestones, we are reflecting on how it has been used and have proposed modifications for the future.

BACKGROUND
Next Accreditation System
To enable the reader to understand how the curricular milestones were developed, it is important to see how they fit into the education system and to review the education terms (Sidebar 1). The Next Accreditation System (NAS) of the ACGME started in July 2013, and it is more appropriately called the “Now Accreditation System.” Developed out of a series of steps (Fig. 1), the NAS shows outcomes of education using modern, efficient tools that are data driven. The milestone evaluations are submitted twice a year and the other metrics are submitted annually, with the intent of limiting accreditation visits to every 10 years. The reporting milestones are based on the six core competencies of medicine, which include patient care, medical knowledge, practice-based improvement and learning, systems-based practice, communication, and professionalism.
General Internal Medicine Milestones

Like the milestones of all of the specialties, the general internal medicine milestones have the six core competencies as the framework.9 Within each core competence, there are subcompetencies, which provide more detail on the activity, knowledge, or behavior that is important to that subcompetency. For internal medicine there are total of 22 subcompetencies. The milestones show the skills required to demonstrate growth from novice to expert on a five-column scale in each subcompetency. There is an overall performance appraisal for each core competency. The goal is that the trainee will be “ready for unsupervised practice,” or achievement of skills in column 4 by the time they are ready to leave the training program (Fig. 2). The clinical competency committee for each program is required to meet twice a year to review the evaluations and make formative recommendations regarding trainee performance. These are shared with the trainee and uploaded to the ACGME. A summative recommendation based on the aggregate of work and milestones that the resident has achieved is made when the resident completes training. The internal medicine milestones that the resident has achieved during residency can be reviewed by the fellowship program director after the resident has started training in the fellowship program.

Subspecialty Milestones

In February 2013, representatives from the ACGME, Alliance of Academic Internal Medicine, ACGME, and sponsoring societies of accredited fellowship programs began the process of defining the reporting subcompetencies for fellows.10 This process was accelerated compared with what had occurred for general internal medicine, but the committee demonstrated substantial solidarity and consensus. There were three meetings, homework, and multiple conference calls. All of the participants agreed that it was important to start all of the fellowships with the same reporting subcompetencies as the general internal medicine milestones. Of the six core competencies, medical knowledge and patient care required most of the changes within the subspecialties. Systems-based practice, practice-based improvement and learning, communication skills, and professionalism are similar for both internal medicine residency and subspecialty fellowship. The number of subcompetency streams was not decreased from general internal medicine in the subspecialty document because of concern that dropping a subcompetency stream early in the process would limit the ability to see differences across the continuum of training. There was discussion about dropping professionalism considering that physicians should have mastered these skills by the time they complete internal medicine, but, in the end, it was maintained because trainees face different stressors in different phases of training. The concept of conflicts of interest, not emphasized in the general internal medicine milestone, was imbedded into professionalism. An additional subcompetency stream called “scholarship” was added. Procedures were divided into two parts: invasive and noninvasive. At the time of publication in 2014, there were 22 subcompetencies milestones for general internal medicine and 23 for the subspecialties. The document for the specialties was labeled the “Internal Medicine Subspecialty Milestones.”

Curricular Milestones

Concurrent to the development of the internal medicine subspecialty milestones (“reporting milestones”), several subspecialties developed curricular milestones. Curricular milestones are granular descriptions of the knowledge, skills, and attitudes or behaviors that define the content of the six general competencies. Curricular milestones can provide specialty specific content that is unique to that specialty. They can function as the program's curriculum and they can be modified to meet an individual program's structure and needs. Because curricular milestones are tailored to the specialty, they can be easier for faculty to use to describe specific skills than the general language in the reporting milestones.

The ASH/ASCO Curricular Milestones were developed collaboratively, with a group that included members of the training program committees from each of the societies and invited guest experts including expert educators from Canada.2,3 The curricular milestones were developed to have a context-specific document that could be linked to the internal medicine subspecialty milestones. The idea was to have content that could be readily recognized by faculty in hematology/oncology. The committee members started with defining the fundamental elements of the specialty, the “entrustable professional activities” that make up the specialty.8 They looked at what was required by the ACGME and the ABIM and included elements from these areas if they were missing. As the list of entrustable professional activities was expanded, they included topics not already noted in the ACGME reporting milestones. The milestone content was designed to provide training that is focused on the unique knowledge, skills, and abilities of the subspecialty, as well as to build on the general internal medicine requirements.11

PRACTICAL APPLICATIONS

- The Next Accreditation System was developed by the ACGME to align training with 21st century care and develop tools that would help streamline the accountability of assessment and training outcomes.
- The milestones are tools that describe the knowledge, behaviors, and attitudes of trainees in the six core competencies of medicine along a trajectory so that trainees and mentors can monitor development as a physician.
- The required ACGME biannual reporting milestones in internal medicine consist of 22 subcompetencies in general medicine and 23 subcompetencies in the subspecialties of medicine.
- In 2013, ASH and ASCO developed the ASH/ASCO Curricular Milestones as a document to serve as the curriculum for the specialty and provided a guide to link these curricular milestones to the ACGME required reporting milestones.
- ASH and ASCO have taken the opportunity offered by the ACGME to reflect on the milestones project and to develop a revised set of milestones that will serve as both the ASH/ASCO Curricular Milestones and the ACGME Reporting Milestones.
activities grew, similar elements were combined whenever possible. Subcompetencies that were unique to hematology or oncology required much discussion because most training programs are combined hematology/oncology training programs. These include apheresis, geriatric oncology, palliative care, wellness, and survivorship. The entrustable professional activities were made to “fit” in the ACGME subcompetencies. Most of the entrustable professional activities were placed in the competence of patient care. To distinguish them from the ACGME subspecialty milestones in patient care, a letter subscript was added. For example, in the ACGME reporting subcompetency, PC2, “Develops and achieves comprehensive management plan for each patient,” the ASH/ASCO Curricular Milestones has letters A to M to define the element in the specialty. Once a draft of the ASH/ASCO Curricular Milestones was completed, it was reviewed by program directors in both societies before being finalized and made available on the respective websites. Webinars took place for faculty development, and the document was discussed at annual meetings and retreats.

LESSONS TO DATE FOR INTERNAL MEDICINE MILESTONES AND SUBSPECIALTY MILESTONES

In December 2017, the ACGME met with representatives of the subspecialty programs to reflect on the internal medicine subspecialty milestones. ACGME staff reviewed data, available in annual reports on the ACGME website, for each subspecialty of the Internal medicine subspecialties. In academic year 2016 (June 2017 data), “straight lining” shows the percent of programs for which all subcompetencies were assigned the same score, implying a problem with
the assessment scale. This occurred approximately 10% of the time in general internal medicine and in the internal medicine subspecialty programs. For hematology/oncology programs, it occurred 20.7% of the time for the F3 year.\(^{11}\)

At the meeting, representatives agreed that the milestones have achieved many of the goals that they set out to achieve. The internal medicine subspecialty milestones include behavioral descriptions with clear anchors,

![FIGURE 1. Development of the Internal Medicine Subspecialty Milestones Document as Part of the Next Accreditation System](image)

**FIGURE 1. Development of the Internal Medicine Subspecialty Milestones Document as Part of the Next Accreditation System**

**FIGURE 2. The Titles and Meanings in a Subcompetency**

A sample format for a subcompetency, showing the format for submission of this information to the ACGME. This is one subcompetency in Patient Care.

The boxes at the bottom of the columns indicate the best fit for the trainee on the milestone trajectory. It is the goal for the trainees to achieve this box by the end of their program.
demonstrate progression of skills achievement, and promote formative feedback. Most representatives felt that there are areas that needed improvement. These included overlapping domains, lack of clarity in many of the paragraphs, and challenges with assessing practice-based improvement and systems-based practice. Column 1, labeled “critical deficiency” (Fig. 2), has variable use. Among the general internal medicine programs, the critical deficiency assessment was used in 100 of 472 programs (21%), but, among the subspecialty programs of internal medicine, it was used in 0% to 6% of the programs.

There are national or multi-institutional validity studies for milestones in internal medicine, emergency medicine, pediatrics, family medicine, and neurosurgery. Data from all U.S. medicine programs for 2013 to 2014 showed that the milestones could provide developmental progression over the training years. Feedback on the milestone process for patient care and systems-based practice from 34 participants of clinical competency committees in internal medicine showed that the milestones were useful in formative and summative feedback. The participants also raised concerns about the length and complexity of some milestones and suggested specific changes. The focus groups also identified a need for more faculty development. Most participants agreed that the patient care and systems-based practice milestones would help competency committees assess trainee progress toward independent practice. A cross-sectional study of United States internal medicine residency programs compared assessments prior to 2015 and after 2015 (when milestones were introduced). Milestones ratings were better at detecting problems with professionalism than the pre-2015 system. Medical knowledge ratings by program directors using both systems correlated with certification scores, but the milestones ratings were better at detecting residents who failed the certifying examination and those who chose not to take the examination. Internal medicine medical knowledge milestones had a tighter correlation with first attempt at licensure examination than the old ABIM-required summary skill score of knowledge.

A small study in hematology/oncology fellowship program showed that the SBP2 subcompetence stream ("recognizes system error and advocates for system improvement") could be used as an assessment tool for systems-based practice. New research is examining the effects of gender on milestones ratings, stringency and leniency, trajectories, program-level effects, and correlation with future practice. The ACGME has faculty development sessions on the milestones in Chicago, Nashville (Vanderbilt University), Los Angeles (the University of California at Los Angeles), and Cleveland. There are now two more sites (Philadelphia and Michigan State University).

SUBSPECIALTY MILESTONES 2.0

The ACGME has suggested the possibility of revision of the internal medicine subspecialty milestones. At the meeting in December 2017, the subspecialty representatives of inter-

ASH/ASCO CURRICULAR MILESTONES 2.0

In the past year, the training program committees of ASH and ASCO also looked at the content of their curricular

SIDEBAR 2. Highlights of ASH/ASCO Curricular Milestones 2.0

1. Curricular Milestones 2.0 was prepared with the intent that it would serve as both the curricular milestones as well as the reporting milestones for hematology/oncology.
2. PC1 (gathers and synthesizes essential and accurate information to define each patient’s clinical problems), was kept because hematology/oncology specialty disorders have unique presentations.
3. Patient care activities that stand out or are unique to the profession were kept as important subcompetency streams such as care of the geriatric patient, ability to manage patients receiving a stem cell transplant, ability to manage transfusions, ability to manage side effects of therapy, comfort and skill in integrating clinical trial research, facility with hospice and palliative care, and care that considers survivorship and cancer prevention.
4. The important skill of recognizing opioid addiction was added.
5. Documenting medical decision-making to include concepts of high value was added.
6. The level of skill a fellow displays as a team leader was emphasized.
7. PC4 (procedural-based skills) was reworked based on the changes to 2018 ABIM procedural requirements.
8. Redundant competencies were merged (SBP1 and ICS2; PBL1 and PBL2; PROF1 and PROF4).
9. Redundant or unnecessary paragraphs were omitted, leaving the document much easier to read.
10. The subcompetency of PROF2 (accountability to patients and the profession) was changed to focus on development of personal and team wellness.
11. Scholarship can be performed in quality and process improvement, educational research, clinical research, and basic research, but the aspirational goal remains publishing in the chosen field.
12. A subcompetency was added to Interpersonal Communication Skills to emphasize communication of plans for systemic therapy and achievement of informed consent for that therapy.
milestones and reexamined the process of linking the data from the curricular milestones to the internal medicine subspecialty milestones. Both groups thought that the presence of two documents was awkward, and the dual documents may have contributed to confusion by program directors and trainees. Meanwhile, the ACGME milestones group had developed draft-harmonized milestones for non-patient care, nonmedical knowledge milestones for all ACGME specialty programs. The program committees for ASH and ASCO revised the subspecialty curricular milestones using the template provided by the ACGME for the non-patient care, nonmedical knowledge milestones, and labeled this new document the “Hematology/Oncology Curricular Milestones 2.0.” The new milestones document revised the language to be as positive as possible, decreased redundancy, and focused the language for each of the skills. The training committees at ASH and ASCO have requested consideration to use the ASH/ASCO Curricular Milestones version 2.0 as both the curricular and required reporting subspecialty milestones. The groups believe that this will result in a more streamlined evaluation process that may clarify assessments for both program directors and trainees, and the change in language will encourage the use of all five columns of the evaluation scale.

Because ASH and ASCO are working with the ACGME and ABIM on revisions, the finalized document will not be available for several months. The major changes that the ASH and ASCO committees have recommended are highlighted in Sidebar 2. To summarize, the group changed the procedural and ASCO committees have recommended are highlighted in Sidebar 2. To summarize, the group changed the procedural and ASCO revised the subspecialty curricular milestones version 2.0. The breadth of the material included can be added to a didactic curriculum and can be a template to use for programmatic assessment and for faculty development topics of ASH and ASCO. By pulling out all of the knowledge, behaviors, and attitudes that we see in our trainees and showing this in the subcompetencies, we hope to help them see their individual strengths and weaknesses, and use the data to improve as physicians and leaders in our field. Aristotle said, “The whole is the sum of its parts.” We can make that analogy here because the new framework enhances clarity of required knowledge, skills, and behaviors for fellows, faculty, and program directors. Thus, the new generation of leaders in our field will be in a better position to understand all aspects and perspectives. We look forward to continuing this dialogue with our community and improving the outcomes of training and patient care.

ACKNOWLEDGMENT

The authors would like to acknowledge all of the committee members for the Curricular Milestones 1.0 and 2.0. We also want to thank Lyndsey Sierra and Michal Tibbits, ASCO staff, and Charles Clayton and Karen Kayoumi, ASH staff.

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The rapid diffusion and adoption of social media has created a new frontier in cancer communication. In contrast to the more traditional communication modes (e.g., newspapers, radios, static websites) where users passively consume content, social media sites (e.g., Facebook, Twitter, Instagram) enable users to interact and collaborate to generate content. This multidirectional, participative discourse has created a host of new opportunities and challenges in oncology. However, there remains a paucity of literature examining how clinicians and researchers can effectively use social media to complement modern oncology practice and research. In this review, we dissect the benefits and risks of professional social media use in oncology and offer several best practices for clinicians and researchers to achieve effective engagement. We also describe how to participate constructively in Twitter conversations at the time of medical or scientific conferences. Additionally, we demonstrate how to communicate appropriately and safely with patients and families online. Finally, we explore the exciting and nascent field of social media research and highlight the need to investigate its potential value in personalized cancer medicine.

**Benefits, Risks, and Best Practices of Professional Social Media Use**

In general, clinicians and researchers can use social media professionally for two purposes. First, social media serves as an information aggregator, helping users stay current on relevant advances in the medical field. Second, social media serves as an engagement tool, helping users to connect with others who have similar interests, to foster collaboration, and to gain support for personal and professional growth. Both of these purposes pose unique risks and benefits that clinicians and researchers must be aware of as they enter the online space.

As an information aggregator, effective use of social media can help oncology professionals obtain reliable, real-time, and relevant medical literature more efficiently than traditional methods (e.g., digging through stacks of journal prints or emails). Among the major social media platforms, Twitter, a microblogging site, provides a way for busy practicing clinicians to keep up on medical research. Similarly, researchers can leverage Twitter to keep up with both updates in their specific field and new research that might not fall within their specialty. Although informed comments and discussions regarding key journal articles can often be extremely educational, clinicians and researchers must be judicious in evaluating medical information that is discussed online. Health information found on social media may be limited in quality and reliability. Medical information is also often promoted by authors who are unknown or poorly identified. Furthermore, the proliferation of social media has made it easier for users to solely follow content that agrees with their established viewpoints, commonly known as the “echo-chamber” effect. To avoid these potential pitfalls,
we recommend that oncology professionals carefully consider the sources of their information when setting up social media accounts (e.g., who are they following and the content of their posts). We recommend that clinicians and researchers follow a diverse set of reputable health organizations, established scientists, or journal clubs to stay current on reliable research and participate in scheduled live-chats (“tweet chats”), where users discuss health-related topics.

In addition to using social media as an information source, oncology professionals can use social networking sites to participate in online communities, listen to experts, and network and communicate with colleagues. In this way, clinicians and researchers can make themselves digitally accessible to the public, allowing them to connect with other professionals for networking, new job opportunities, and collaborations. Virtual and live professional relationships, collaborations, and friendships have come out of social media engagement. Additionally, social media can help break down traditional barriers to interaction between health care professionals (e.g., professors, residents, medical students, nurses) as well as between providers, scientists, patients, and caregivers. Formal or informal “tweet ups” (the actual face-to-face meeting of Twitter users to solidify the relationships formed online) may lead to mentoring and collaboration opportunities.

Although social media can be a powerful information aggregator and engagement tool, there are some unique challenges and drawbacks for oncology professionals to consider. First, clinicians must be vigilant of the clinician-patient boundaries online; we recommend that public acknowledgment of these relationships be avoided. Second, clinicians must respect patient privacy in online discussions or posts, recognizing that the Health Insurance Portability and Accountability Act (HIPAA) and Health Information Technology for Economic and Clinical Health (HITECH) regulations apply to online environments the same way they apply inside the medical center. Even when information is de-identified, there have been instances of a health care professional losing their job or licensure due to posting online content that had the potential to identify a specific patient. Finally, clinicians and researchers must be aware that their online profile significantly affects their professional reputation; what you tweet, blog, or post publicly represents you. Online content is discoverable and may be used in malpractice cases. People expect clinicians to be composed, calm, and reliable; we recommend a professional and measured tone in all your public online content.

Table 1 summarizes some of the benefits, risks, and best practices for clinicians and researchers who wish to use social media professionally.

## STRIKING THE RIGHT TONE: OPTIMIZING THE USE OF SOCIAL MEDIA DURING CONFERENCES

Twitter engagement at medical conferences marks a new era in dissemination and implementation of research in oncology. The practice of live sharing conference information using Twitter has been increasing in popularity. At the ASCO annual meetings, for example, the number of meeting-related tweets increased ninefold from 7,746 to 72,698 over 5 years (2011–2016). Similarly, an increase in meeting tweets has also been seen at hematology, breast surgery, emergency medicine, urology, radiology, and other medical meetings. The number of unique health care conference hashtags registered by Symplur, a healthcare social media analytics company, has increased from 1,428 in 2014 to 2,282 in 2016.

There are several reasons why cancer clinicians and researchers should consider engaging on Twitter at the time of medical meetings. Annual meetings serve as a forum for the exchange of ideas and dissemination of new research findings. Social media can be a low-cost, widespread, and effective way to share information with the organization’s members, as well as anyone else interested in the content such as providers in overlapping specialties, patient advocates, and the media. Twitter brings together physical attendees with virtual ones, acting as a channel to deliver information from the conference podium to thousands of interested participants who wish to learn, dissect, and provide critical analysis remotely. These interested parties have the ability to “attend” in real-time and contribute to rich discussions at the meeting without delays in information acquisition.

Another benefit of using social media at meetings is that it can provide clinicians and researchers with a more effective learning tool, enabling richer conversations about the research being presented. Conferences are traditionally held in a “classroom-style” format. However, studies have
shown that “push learning” is not the most effective method of adult learning.24 The rapid pace and microblogging characteristics of Twitter are conducive to a learner-initiated style of education.15,25 In utilizing a designated conference hashtag (e.g., #ASCO18), an ongoing Twitter conversation allows for a real-time “backchannel” discussion among attendees, presenters, and others interested in the content.26 Tweets or “little gems” of information being shared can also help one focus on the key learning objectives from each session.26 Diverse points of view can be brought into the discussion, thereby expanding the knowledge base of the participants. Clinical relevance or possible limitations of new research studies can also be discussed and debated, and meeting faculty can join the conversation, taking their presentation beyond the podium. With a sufficient number of engaged tweeters, misinformation and misinterpretation of podium presentations can be corrected quickly, in real time.14 Furthermore, use of conference hashtags allows online meeting discussions to be archived for later search and review. Oncology professionals can also gain insights from sessions that they were unable to attend. Some attendees use their tweets as their notes,19 a form of “microlearning.” Focusing on small bits of content in such a way helps users digest findings of new research. Reviewing conference tweets at a more leisurely pace can serve as a prompt for the user to seek out more information about a particular topic of interest, and this may be a more effective way of learning than relying on the “push” technique of education exhibited in most conferences.27,28

Although there are many benefits for clinicians and researchers to engage on social media at the time of medical meetings, concerns have been raised about the potential for widespread dissemination of information that may not be peer reviewed (such as unpublished abstracts), copyright infringement and intellectual property violation, as well as distraction of meeting attendees by slide photography and digital activity.15,29,30 It may be difficult to convey scientific information in a short tweet which may lead to “incomplete and/or incomprehensible” tweets.29 It has also been demonstrated that with increasing conference tweet volume, there is an increase in activity from “low quality” accounts (such as automated spam or “bot” accounts). In addition, retweets may be purchased from third party entities. These activities can have a negative impact on the quality of the online conversation, decreasing the optimal “signal to noise” ratio, and raises additional concerns about spreading false and inaccurate information.21,31

Despite some of these concerns and cautions, however, social media engagement at the time of medical meetings can be a valuable way for cancer clinicians and researchers to share information and develop new relationships. In Table 2, we outline some of our recommendations on how attendees, presenters, and organizers can participate constructively in Twitter conversations during these events.6,13,15,16,32-36 Dissemination of information at medical and scientific conferences can be enhanced by robust Twitter discussions. It remains unknown how best to evaluate and ensure the quality of conversations taking place; future research is needed to develop metrics that measure the value of these online conversations.6,37

**WHEN YOUR PATIENT “FRIENDS” YOU: APPROPRIATE COMMUNICATION WITH PATIENTS AND FAMILIES ONLINE**

As social networking sites such as Facebook and Twitter grow in numbers of active users, and as more online patient communities (e.g., Inspire.com, Smart Patients, Patients-like-Me, and Cancer Support Community) become available,

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**TABLE 1. Beneﬁ ts, Risks, and Best Practices of Professional Social Media Use**

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Social Media as an Information Source</th>
<th>Social Media as an Engagement Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Keep current on medical research that is generating interest</td>
<td>• Promote work and ideas that you consider important</td>
<td></td>
</tr>
<tr>
<td>• See the same medical news that appear in patient news feeds</td>
<td>• Comment on or reduce misinformation</td>
<td></td>
</tr>
<tr>
<td>• Learn from online discussions about key studies and research</td>
<td>• Build professional connections for networking and collaboration</td>
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<table>
<thead>
<tr>
<th>Risks</th>
<th>• “Echo-chamber” effect</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>• Click-bait articles</td>
</tr>
<tr>
<td></td>
<td>• Increased potential for the spread of misinformation</td>
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<td></td>
<td>• Time management</td>
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<th>Best Practices</th>
<th>• Avoid importing contacts from external sources</th>
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<tr>
<td>• Join live-chat hours and/or journal clubs on Twitter</td>
<td>• Profile and bio should mirror professional role</td>
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<td>• Follow reputable accounts that demonstrate extensive experience in your topic of interest</td>
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<td>• Avoid only following individuals and accounts that you tend to agree with</td>
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<tr>
<td>• Vet information you redistribute or promote</td>
<td>• Establish personal ownership of activity and views</td>
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<td>• Always remember what you tweet, blog, or post publicly represents you</td>
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**TABLE 2. Social Media Engagement Best Practices**

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**TABLE 3. Risks and Best Practices of Social Media Use**

<table>
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more opportunities exist for clinicians to connect and communicate with patients outside of the clinic.38 Engaging through social media creates opportunities for clinicians to publicly demonstrate their compassion, medical expertise, and passion for healing. This may also serve to enhance trust in the medical profession.39 However, the limits of appropriate health professional interactions with patients and caregivers online may sometimes be unclear.

Some professional societies have issued guidelines that aim to provide direction for physician communication with patients in the online space.40,41 The American Medical Association, for example, advises that physicians be aware of standards of patient privacy and confidentiality, refrain from posting identifiable patient information online, and if interacting with patients online, physicians must maintain appropriate boundaries of the patient-physician relationship. The American Medical Association further guides that to maintain appropriate boundaries, physicians should consider separating personal and professional content online.40 The American College of Physicians (ACP) and Federation of State Medical Boards (FSMB) issued a joint policy statement that, while acknowledging that there are benefits to social media in health care, advised against engaging with patients in social interactions online. They recommended that physicians not “friend” or contact patients through personal social media.41 Similarly, the American Congress of Obstetricians and Gynecologists guidelines, published in 2015, recognized that physicians should use discretion in accepting friend requests through social media rather than issuing a blanket statement opposed to it.42 Furthermore, ASCO has a “Ten Tips for Use of Social Media” and encourages physicians to get involved and to be engaged, but it also guides physicians to maintain professionalism in the online setting by protecting patient privacy and avoiding impropriety.43 Similar to the ACP-FSMB guidelines, ASCO also advises that a professional distance is maintained between the health care professional and the patient, both in person and online.

Despite the clear-cut nature of professional society guidelines, uncertainty arises in real-world clinician-patient relationships (Table 3). Friend requests from patients on Facebook create a unique dilemma for physicians. In a survey of 187 Australian physicians, 19% reported receiving a friend request from a patient.44 One of the potential risks of communicating and connecting with patients through social media, including accepting friend requests from patients on Facebook, is the blurring of the boundaries of the clinician-patient relationship, potentially jeopardizing the therapeutic relationship.45

As professional guidelines recommend, clinicians should maintain appropriate boundaries for the clinician-patient relationship and should not share information that could jeopardize patient privacy. Health care institutions may have their own social media policies or guidelines for their clinical employees; it is advisable to be aware of these.46 Clinicians and researchers should consider establishing professional social media profiles, such as on Twitter or Facebook, to interact and communicate with the general public. Many health professionals, like much of the general population, have personal Facebook profiles,44 and privacy settings on profiles can be modified to increase user privacy. For example, privacy settings can be set to show only a limited amount of information to specific groups of people, to limit who sees the profile in a Facebook search, and to limit friend requests or messages to only those with whom a mutual friendship is shared.

It is advisable for cancer clinicians and researchers to have a plan in place for how to handle friend requests from patients or caregivers. One potential solution is to decline the friend request and to consider advising the patient, “I have a personal policy not to connect with patients or their family through Facebook.” If a patient asks an oncology professional for medical guidance on an online social networking platform (e.g., Twitter, Facebook, blog), it is reasonable to provide the patient with credible online resources (e.g., peer-reviewed cancer-related information such as Cancer.Net). It is also reasonable to decline to give specific medical advice and refer the patient to speak with his or her own physician directly.

Studies and anecdotal reports of what physicians and patients believe to be appropriate when a patient friends a

<table>
<thead>
<tr>
<th>Stakeholder</th>
<th>Best Practices</th>
</tr>
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</table>
| Attendee | • Create a professional Twitter profile  
• Include a photograph, brief biography, and affiliation  
• Use the conference hashtag (e.g., #ASCO18)  
• Use disease-specific hashtags (e.g., #BCSM)  
• Include appropriate credit and citation in tweets  
• Distinguish one’s own opinion from that of the speaker  
• Tweet to share information, not to recreate the conference |
| Speakers/ Presenters | • Include twitter handle on presentation slides  
• Consider use of PIGLETS (presenter-initiated and -generated live educational tweets) to amplify message  
• Engage in postpresentation dialogue online |
| Conference Organizers | • Develop, register, and promote hashtags prior to the meeting  
• Post social media policies online and in printed meeting materials  
• Include Twitter names on faculty biographies and meeting badges  
• Identify key meeting attendees with an active Twitter presence to serve as leaders in the online discussion (e.g., ASCO’s Featured Voices)  
• Proactively identify and tweet key slides from presentations  
• Organize an in-person “tweet up” social event to help those who have been interacting online get to know one another in person  
• Use the conference hashtag (e.g., #ASCO18)  
• Include appropriate credit and citation in tweets  
• Tweet to share information, not to recreate the conference |

### TABLE 2. Twitter Etiquette and Best Practices at Medical Meetings
TABLE 3. Scenarios and Recommendations on Handling Online Clinician-Patient Boundaries

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Recommendation</th>
<th>Example Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Patient</td>
<td>You have a personal Facebook page and you receive a friend request from a woman you are currently treating for cancer.</td>
<td>Recognize that accepting the friend request may blur the patient-physician boundary. Consider declining the request.</td>
</tr>
<tr>
<td>Former Patient, Not in Your Practice</td>
<td>You receive a friend request from a patient you treated for cancer more than 5 years ago and discharged to primary care at the completion of 5 years post-treatment.</td>
<td>If no formal patient-physician relationship exists, it may be acceptable to accept the friend request. Clinicians can use their judgment whether to accept or decline.</td>
</tr>
<tr>
<td>Facebook Friend and Active Patient</td>
<td>One of your current Facebook friends is diagnosed with cancer and he is now under your care as a patient. He sends you a Facebook message to ask you about some side effects he is having from his treatment.</td>
<td>Since a formal patient-physician relationship now exists, consider directing the patient to official, established channels for proper communication, such as calling the office or use of the hospital or clinic’s electronic patient portal.</td>
</tr>
<tr>
<td>Patient, Not in Your Practice</td>
<td>A person on Twitter who follows your professional Twitter profile sends a tweet to you asking what screening tests you would recommend for her since she carries a BRCA mutation. You both have public accounts, so this tweet is visible to the public.</td>
<td>Avoid giving specific medical advice but feel free to share reputable online information resources (e.g., peer-reviewed websites and other credible patient education sites). It is also reasonable to decline to give specific medical advice and refer the patient to speak with his or her own physician directly.</td>
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The role and value of social media in cancer research

Social media represents an extremely promising frontier for cancer research. Although there is a dramatic growth in the popularity of social media among health care stakeholders, there remains a paucity of literature to suggest that these new, participative communication channels are improving health outcomes. Thus, there is a gap in knowledge about the value and direct application of social media platforms in oncology.

Social media has opened new areas of research with potential applications in oncology. First, social media may be used as a data source to study cancer communication to improve precision medicine. Similar to mining the genome to discover the links to a patient’s phenotypes and identify targetable drugs that can alter the disease course, mining...
social media data may be a new frontier for personalized or precision medicine (Fig. 1). Although much of the traffic online might seem superficial or lacking the gravitas of our genome, mining the social media data for exposures and behaviors might radically personalize the delivery of health care. Several public health researchers have recently described the potential of using social media data sources to evaluate public communication about health. Sinnenburg and colleagues, for example, were able to computationally aggregate and analyze 4.9 million tweets related to cardiovascular disease, characterizing tone, style, and perspective of these tweets, as well as some basic demographics of the users posting them. They concluded that Twitter has the potential to reflect real-time discussion about cardiovascular disease, and that characterizing these conversations may help differentiate between signal and noise. Numerous other observational studies have been done to examine the content on platforms like Facebook and Twitter related to cancer. In this way, social media may be used as a “data set” to track and identify communication inequalities and examine modes of communication used by individuals, communities, and population subgroups. It can also be used to monitor public beliefs, attitudes, and social norms; capture reported behaviors related to cancer; and evaluate media effects on individual or population health.

Second, social media may potentially be leveraged as an intervention (or part of an intervention) to change behavior or outcomes. Several studies have examined social media interventions for smoking cessation, mental health disorders, HIV prevention and treatments, and recruitment for medical research. Although many have speculated about the potential utility of social media for cancer clinical trial recruitment, the Metastatic Breast Cancer Project is one of the first nationwide studies that used social media as a recruitment tool, demonstrating that social media can rapidly identify and enroll large numbers of patients willing to share tumor, saliva, and medical records. Further research, however, is needed to measure the influence of social media interventions (e.g., online support groups, video sharing and educational communities, trial recruitment efforts) on health, behavioral, or clinical outcomes.

There are important ethical and legal challenges that clinicians and researchers must be mindful of when conducting social media research. Currently, there is a lack of clear guidelines for health research with regards on how best to engage patients using social media interventions in a way that is ethical and generative. Mining of social media data needs to occur in a way that is transparent to patients’ and consistent with their preferences for privacy. For example, informed consent is difficult to obtain from individuals who contribute content to large, public data streams such as Twitter or Facebook. The sharing and analysis of social media data may thus make potential patient privacy violations more likely. Furthermore, social media platforms often have demographic patterns that are not consistent with the general population, which may compromise the principle of fairness in research subject selection and generalizability in terms of research findings. To mitigate the risk to patient autonomy, respect, and confidentially, research-related activities on these platforms require careful review by the institutional review board.

Another major challenge in social media health care research is securing adequate funding. The use of mobile technology and social media tools in research has increased 384% in the past decade, but this field still reflects only about 1% of National Institutes of Health expenditures.

Although funding for this type of research has increased in both quantity and scope from 2005 to 2015, we believe that further funding opportunities are needed to encourage investigators to focus on this emerging field.

Social media represents an extremely promising frontier for cancer research, however, currently it is in early
proof-of-concept stages. We must enhance our ability to collect and interpret information from social media platforms, link the information available with validated clinical data, develop interventions that impact behavior and outcomes, and operate consistently with patients’ preferences for privacy. We must learn how to decipher the signal from the noise, understand the limitation with generalizability of findings from social media research, and develop standard methods that promote ethical, accurate, and relevant work in this field. As described by Dunseath and colleagues, we are embarking on a period where research can be designed to enroll 10,000 to 1 million participants (e.g., National Institutes of Health’s All of Us Research Program, Google’s Baseline, Apple’s ResearchKit).68 This may lead to significant advances of Health’s All of Us Research Program, Google's to enroll 10,000 to 1 million participants (e.g., National In-
are embarking on a period where research can be designed in this field. As described by Dunseath and colleagues, we methods that promote ethical, accurate, and relevant work fi ndings from social media research, and develop standard the noise, understand the limitaƟ  on with generalizability of

CONCLUSION
In this article, we describe how clinicians and researchers can effectively use social media to complement modern oncology practice and research. This includes building a professional social media presence to engage with other users and stay current with the literature, leveraging social media at academic conferences to generate richer and more educational discussions, navigating social media to appropriately and safely communicate with patients online, and examining social media as the subject of population health research. Further research, collaboration, and funding are needed to improve the evidence base for how we can eff ecƟ  vely leverage social media to engage patients, providers, and communities to improve health behavior and outcomes. We encourage oncology professionals to take the first steps in exploring this new frontier of oncology.

References


Caring for Colleagues and Loved Ones With Cancer

John W. Cook, Melissa Dillmon, MD, Stephanie L. Graff, MD, Rebecca D. Pentz, PhD, Ranjana Srivastava, MBBS, FRACP, and Julia L. Close, MD

OVERVIEW

Throughout the arc of a career in medicine, physicians are universally faced with the difficult decision of when to provide care for a colleague and when to refer to another physician. Gauging the magnitude of your relationship, both professionally and personally, and then weighing how to add the roles of physician and patient to your preexisting relationship is complex. We review and discuss care of family and colleagues, address ethical boundaries both firm and flexible, and explore the emotional weight of those relationships.

“I want you to be my doctor,” said the voice on the phone. It was an unexpected call from my therapist, Lisa (a pseudonym). I had been seeing her for several months to cope with peripartum depression after the birth of my third child. We had made a lot of progress, and I felt back to my old self. She didn’t usually call me.

“I’m in the hospital. I’ve got lung cancer. That’s your specialty, right?”

She was testing me, right? She and I spent a lot of time on boundaries, and certainly treating your therapist for cancer crossed one. How could I have a patient-doctor relationship with someone who knew so much about me? How could I ever be objective in caring for her? How could we switch places in the treating relationship? I let her know I needed to think it over.

Shortly after, the fellow on the consult team called me, asking me to overbook Lisa into my clinic after visiting her in the hospital. “I told her what a great doctor you are, and she said she definitely wants to see you.” “Did she mention she knows me?” “No. She knows you?”

At that point, my mind raced a little. How could I let Lisa down? She had gotten me through so much. On top of letting Lisa down, could I just tell the fellow to book Lisa with someone else? Should I just be open and talk about my recent depression?

Later that evening, I visited Lisa in the hospital. I sat down and explained that I could not take her on as a patient. She said, “I’m proud of you. You’re right and I was scared. I should never have asked.” We had a very social visit, and I answered some vague questions about cancer, letting her know I had not reviewed her chart and had no plans to. I contacted the attending physician of record and asked him to have her follow up with another thoracic oncologist.

With hindsight, the decision to refer to a colleague seems straightforward. At the time, it was a considerable challenge driven by the desire to help someone who was so close to me. I work in a large health care system in which there are many other providers to offer care. Had I been in a different setting, there may not have been that option. (Julia Close, MD)

There are many scenarios we face as oncologists when we must consider whether it is appropriate to care for someone. The American Medicine Association’s Code of Medical Ethics clearly states that physicians should not treat themselves or members of immediate families. Outside of this clear guideline, we must each make a decision on the basis of our ability to provide appropriate care to the individual. In the case of a colleague, friend, or “VIP,” we must consider our ability to be remain objective in care.

If I agree to care for my colleague, my best friend, or my child’s teacher, will I offer that individual something different than I would offer a patient I do not know well? Will I be more aggressive? Less aggressive? Will I fail to see my own bias in the relationship? Will I be able to transition care when appropriate, or will my own grief get in the way? Will the patient be able to be open with me to provide personal care?
information needed for care? Can our current relationship transition to a doctor-patient one?

To successfully navigate these scenarios, there are not only ethical considerations but practical ones. How do we lay ground rules to ensure success in this new aspect of the relationship? Although the American Medical Association’s Code of Ethics states that physicians “generally should not treat themselves or members of their immediate family,” it does recognize that there are minor care or emergency situations for which another physician is not available, and in these cases acute care is appropriate. An example of this is a rural physician whose family member needs an emergency surgery, and no other physician is present to perform it. Under these circumstances, it would be ethical for the physician to treat his family member because of the urgency of the situation. When it comes to prescribing drugs, physicians should never prescribe controlled substances to family and friends.

Physicians in small towns or rural settings may find it difficult to differentiate whether a person is a friend or a patient first, as they are more likely to interact with the same people for whom they provide care. However, there is a distinction between a close friend, with whom a physician has a personal relationship, and a neighbor or friend with whom the physician interacts only in social settings. The main ethical concern centers on the practice of informal and undocumented care outside of the clinical setting for friends with whom there are close personal relationships. Although one should rarely treat friends and families, it is ethically permitted to treat colleagues, with whom you have professional relationships. If you feel that the relationship is more personal than professional, follow the guidelines for friends and family. Special considerations when caring for colleagues are detailed in Sidebar 1.

When treating a colleague, it is imperative, prior to beginning treatment, that you be comfortable accepting such a role and can provide care in an objective and professional way. If you feel uncomfortable accepting such a role or you find yourself unable to maintain clinical objectivity, suggest another physician with whom you and your colleague both feel comfortable assuming care. When examining a colleague, it must take place in a formal clinical setting and should not be done as a “curbside consultation.” Farrell et al suggest that physician–patient often do not reveal their complete medical histories, specifically substance abuse, or psychological disorders, in a curbside setting. So once you have agreed to treat a colleague, the examination should take place during a formal office visit at which a complete physical examination can be completed and a complete medical history can be obtained. Although patient autonomy is of the utmost importance in patient care, it is crucial to present your own formal treatment recommendation, because the colleague may not have as much expertise in the relevant field of medicine as you. It is imperative, when treating a colleague, that you treat his or her medical information with the utmost confidentiality. You should not discuss the information with any other colleagues, unless you have been given permission by the patient.

In the following case study, Dr. Melissa Dillmon provides a first-hand account of a successful case of treating a colleague.

Countless books and papers have been written about the doctor-patient relationship, but there are very few resources for physicians to turn to when they are faced with the difficult situation of caring for one of their colleagues or partners. Although some physicians may choose to refer their friends and partners to clinics nearby, a small-town practitioner often does not have that option. During our careers, it is likely that a colleague will approach you and ask you that very scary question, “Will you be my doctor?” Why does that question fill us with immediate trepidation? It is important for physicians to contemplate how they would respond before that day occurs. As a physician, one should ask oneself, what is it that I fear in taking care of a colleague, what are the real dangers to taking care of a partner, why did they choose you, what are their expectations of you and what are your expectations of yourself, and what can you gain or learn from this experience?

Ten years ago, I was a new partner in my multispecialty group. I had been in practice a little more than 2 years when a colleague approached me and asked me to be his physician. Tony was a pulmonologist whom I had gotten to know in those first 2 years as a fierce advocate for his patients.

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Adapted from Table 1 in Farrell et al.3

SIDEBAR 1. Special Considerations When Caring for Colleagues

• Consider whether care can be provided objectively
• Maintain confidentiality
• State that potentially embarrassing aspects of medical may need to be addressed for optimal care
• Do not allow location of care to compromise quality
• Clarify the role of the colleague as the patient
• Clarify the cost of care at the beginning of treatment
• Document all encounters, as even informal consultations can result in malpractice claims
• Be aware some states prohibit caring for colleagues
had been a physician champion for patients with lung cancer and insisted that we could improve their outcomes by working together as a team. He was the driving force behind the creation of a tumor board that met every Monday night to prospectively discuss and debate case after case. We came to this conference for our patients but also out of respect and fear of Tony. He came to me prior to sharing his diagnosis with the rest of his colleagues and asked me to be his physician after he was diagnosed with stage IV lung cancer. “What is the irony?” he asked.

I asked why he chose me. He told me he that he chose me not because of my superior knowledge, my recent training, or my personality but because I had known him the least amount of time, and it would be easier when he died on me than my partners. He was wrong in this one thing. Tony had been through cancer before. When he was a medical student, he was diagnosed with Hodgkin lymphoma, and the radiation he had received then was likely the cause of his lung cancer. I was scared to be Tony’s physician. I was fearful of caring for a man whose intellect I admired and who was held as a pillar within our clinic. He was a physician’s physician. I also feared that he might try to manage his own care or dictate his treatments. I worried I would be in the spotlight and blamed when things inevitably went bad. I had realistic expectations of what I could do for him, and thankfully he did as well.

Tony proved to be an easy patient. He never questioned my clinical decisions or challenged my recommendations except when I recommended that he receive radiation to his central nervous system metastases. He would never go down that path again. He asked me to get him to his daughter’s law school graduation, and that was all he expected. I think the fact that he was able to go to her graduation was due more to his determination than to my treatment.

Toward the end of Tony’s life, his keen intellect began to fade, and this was very hard for him to accept, but he did it with grace. I saw his partners in our clinic who had known him for decades put their practices aside and take time to spend with their colleague. I saw a small-town community that loved their doctor weep as those they had known for decades put their practices aside. Friends and colleagues, I will experience more pain as we walk together through their journey. Five years ago we dedicated our new cancer center, and it is rightfully named after Tony. He gave an enduring legacy to this community, and I hope in exchange that I was able to give him the best care I could provide, the respect he deserved, and the graceful death he was due. (Melissa Dillmon, MD)

An issue that is rarely discussed is what special privileges one can ethically offer colleagues or patients who are considered “VIPs.” Farrell et al suggested that one avoid offering special privileges to colleagues such as bypassing office staff members. Yet this kind of special privileging is common. You tell your colleague, “Just text me, and I will work you in for an appointment.” Or your colleague emails you directly with a question, and you answer promptly. Or the institution has an employee appointment phone number so that all employees get privileged access to appointments. I suggest that as long as these behaviors do not disadvantage other patients in a meaningful way, they can be ethically supported.

Common-sense morality holds that we have special obligations to people with whom we are in relationships, though the exact moral framework that grounds special obligations is debated. The argument is simple enough: inherent in being in any relationship are certain obligations that are beyond those we owe all humans. Parents have obligations to care for and nurture their own children in ways not required of them for other children. I have argued elsewhere that siblings have obligations to donate stem cells to siblings, whereas strangers do not. The list of those with whom we have relationships that spawn obligations typically includes friends and colleagues, and sometimes compatriots. Surely the special obligations to colleagues are moderate compared with the obligations of parents to their children, but they are extensive enough to include taking a text from a colleague and fitting him or her into your schedule, if other patients’ care is not jeopardized. Relationships are built on trust, mutual respect, and honesty, but they also involve shared experiences, such as sharing a workplace and its responsibilities. They also involve special obligations, which can include some special treatment when one is treating a colleague, as long as other patients are not jeopardized, and the guidelines outlined above are followed.

The daily grind of making tough decision in clinic and having the somber conversations with patients and their families can lead to even the best clinicians’ burning out. This burnout can also lead to a slip in the ethical integrity that must always be practiced. There have been many different ways clinicians have coped with these feelings. Some of these methods are very simple, others elaborate, but sometimes it is the simplest that can lead can be the most therapeutic. In the following story, Dr. Ranjana Srivastava offers a simple method that has allowed her to continue her excellent work in an area and population that needs dedicated clinicians.
At the sight of a new patient in clinic, I react with a familiar feeling, trepidation. My public hospital is located in a region that has become a hub for migrants and refugees. It boasts delicious food, diverse culture, and the generosity of strangers. It is also a place of poverty, extreme disadvantage, poor literacy, and unrelenting need. Here, early cancer may be curable, but the personal devastation wrecks lives in ways one can hardly imagine.

My patient listens quietly as we discuss her locally advanced breast cancer, the need for downstaging, the toxicities of chemotherapy, and the logistics of travel. In halting English, she asks sensible questions and shows the resilience that is so often the trademark of people who have fled war and persecution. They were both professionals back home. Her husband, in more fluent English, wistfully asks what would have happened if she had had the ultrasound 6 months ago when it had been recommended. It’s hard to say, I say, as regret washes over me at the feel of her lumpy axilla. But you are here now, and we will look after you. They nod gratefully. Generating a chemotherapy order is the easiest part and the part that I can control, but holistic care of patients requires more than a chemotherapy script. She needs a social worker urgently if her husband has to reduce his hours to care for the children. Depending on his work schedule, she will need patient transport. And an interpreter. An occasional counselor would be useful, especially in the first few weeks. She would dearly like her mother to come over, but the visa process will be long and painful. Fatigue will limit her ability to do housework and childcare; she may need community volunteer support and help from the children’s primary school.

I talk her through all of this and am impressed by her calmness. An hour later, there is one more thing left. “We will have to find a way of giving an injection into the skin, called GCSF.”

“I know how,” she offers.

“You do?” I say, relieved.

Suddenly, the tears start, and as I wait politely, and uncomfortably, they become a torrent.

“My eldest child is diabetic and I do all her insulin. I don’t care if I die but what will happen to her? Who will manage her diabetes? Who will remind her to eat? How will she cope?”

I listen in dismay. Racking my brains, I tell her that once she begins treatment, I can reach out to the school, but by this point, all I really want to do is to make it all better. All of it. Her refugee status, her serious diagnosis, the fraught journey ahead, her husband’s meager income, her children’s bewilderment, her daughter’s diabetes. After all, how much misfortune can one person bear?

Finally, my patient leaves, bestowing far more gratitude on me than I deserve. I am glad I was able to reassure her, but I have been here before with hundreds of patients, and I know that even in ideal conditions, this journey is fraught, physically and emotionally. That whole week, her story plays on my mind. Did she sleep that night? What did she say to her children? Did she call her parents or spare them the trauma for now? How does a traumatized refugee deal with the trauma of cancer: better or worse? Somewhere along the line, her story merges with mine. She is my age, her kids are like my kids, her busy household stumbles along like mine: where is the room in life for sudden and major shifts?

And yet, ironically, I remind myself, she is not even the worst off in the cohort of vulnerable patients. There is the man whose wife couldn’t cope in a new country and went back to her war-torn village, leaving behind young children and a custody battle. The woman whose husband abandoned her to the mercy of strangers as soon as they reached safety. The dying man who had to choose which child should fly to visit him, but the visa was denied anyway. The lonely student who refuses to hear that her recurrence is incurable and clings to the hope of medicine in a first-world country instead of going home to die. Some days, I have to convince myself that success stories ever existed in this patch of human suffering.

The ancient Roman orator Cicero observed that “a tear is quickly dried, especially when shed for the misfortunes of others.” Perhaps this is true for the person who rarely encounters misfortune, but the very job of an oncologist is to sit with many simultaneous misfortunes and carry undried and unshed tears. Over time, the weight of such tears and fears grows so heavy that the enthusiasm and joy of practicing medicine curdles to dread.

Like many oncologists, I struggle to keep up with the reams of data emerging about cancer treatment, especially in the era of a seeming breakthrough a day. But the challenge of being an oncologist is not so much in keeping up with the science of oncology but in honoring its art. The science fix comes relatively easily from keeping up with journals, talks, and conferences, but the art of oncology lies in letting oneself feel the fears, anticipation, happiness, grief, hope, and disappointment of patients, sometimes all in the course of a day, and still having the strength to return to work day after day, year after year.
Some time ago, following an emotionally demanding run at work, I took the Maslach Burnout Inventory, a psychological self-assessment tool, on which my score reflected a high level of burnout. I responded as any sensible person would: I became a serial test-taker, and churned through the Copenhagen Burnout Inventory, the Oldenburg Burnout Inventory, and many other questionnaires before concluding that perhaps the tests weren’t lying. It took me another few weeks to see someone. Physicians are fortunate to have access to professional help; I found my visit therapeutic and validating. Like many oncologists, my risk of burnout remains high, but I have developed a greater awareness of my emotions and a greater preparedness to protect myself.

Caring deeply for patients is hard work, but it’s also what sustains us. The good physician will never abandon empathy but must find a way to navigate a career that is full of requests, demands, dilemmas, and decisions, all of which can add up to a great emotional toll. My coauthors in this article have suggested valuable ways of negotiating this toll. I would like to add my thoughts about the important role that writing a journal has played in my life.

I have always believed in the importance of debriefing but discovered quite early how difficult it can be. It requires making time, demonstrating vulnerability, and finding a good listener who is not stumped or saddened by the types of emotions that oncology elicits. Meanwhile, I realized that self-reflection was private, readily available, and could be practiced regularly.

There is no “best” way to reflect, but what has worked for me is continuing a daily journal that I started writing in middle school. Along the way there have been temptations to give up, including medical training, having children, and the calls of a busy household. But I have always returned to the powerful pull of writing for the calm and equanimity it induces. Writing is a cheap and ever-ready way of helping me make sense of my world and often does away with the need to debrief with someone else. It helps me sift through emotions and understand my reactions and motivations. Writing a journal doesn’t have to be a big deal; neither does it have to be a daily job if you don’t want it to be. Consider keeping a journal by your bedside so it’s within easy reach when you do feel the urge to unload your emotions. I type much faster than I write; while for essays, columns, and books, I turn to my laptop, I have always used nicely bound books and a good pen for my journals. There is something meditative about writing by hand.

I had never really thought that writing would be anything more than a tool for personal growth, so it has been a wonderful adventure to have gone on to write several books and, for the past few years, a fortnightly column in the Guardian on medicine and society. This column is published in Australia and featured on the Guardian’s international sites in the United Kingdom, United States, and other media outlets. Having a public platform is great, but the responsibility is real. I have used the platform to raise public awareness of health issues, ponder ethical dilemmas, and highlight important research. But I have intentionally and often written about the emotional toll of medicine on the provider because I think it’s only through highlighting these issues that we learn to deal with them. This is not to diminish the experience of patients but rather to explain why a career widely regarded as impressive, honorable, and prestigious can still hurt. I have written about being dumped by patients, being the subject of a lawsuit, and the awfulness of knowing I have wronged someone. I have also talked about depression and suicide, misuse of power, arrogance, bullying, and harassment. In medicine, one seems to trip over stories. Writing sensitively about these events informs others but also succeeds in debriefing the self. The act of writing is good for suspending judgment and aiding perspective. I have found this to be particularly true of writing essays for the New England Journal of Medicine, where expert editorial remarks have really helped me clarify my thoughts. For me, writing has also been an opportunity to help others debrief and reflect. I am always grateful to receive notes and emails from physicians to say that my writing resonated with their own experience; in a small way, it’s nice to be a part of the healing of others.

But although I enjoy writing for the public, what I am most grateful for is the habit of writing itself. In addition to loved ones and colleagues, writing has helped me celebrate, reflect, challenge, debate, muse and mourn. It has helped me understand myself and others. The writer Anaïs Nin described words as a lens to focus one’s mind. I would agree that writing has helped me focus my mind on the job I most cherish: being a doctor to my patients. (Ranjana Srivastava, MD)

The ethical gray area that surrounds the decision of whom to take on as a patient, and how to treat that person, can be simplified into three basic guidelines. First, physicians should not treat or prescribe medication for family or close friends and may treat them only in case of an emergency. Second, when deciding if treatment of a colleague is appropriate, you must decide whether the relationship is personal or professional; if it is professional, you may treat the individual, but if it is personal, you should follow the guidelines for family and friends. If professional, you must decide whether you can be objective, and if there is any hint of worry in that regard, refer to someone else. Third, one must
never provide informal and undocumented care outside of the clinical setting to friends, family or colleagues. You must provide the same level of care you would provide for any patient, not omitting any sensitive test or question. Last, the mental clarity of a physician is most important to helping a physician make ethical decisions in the practice setting. Following the advice of Dr. Srivastava is one of many ways mental clarity can be accomplished.

References


SARCOMA
Neoadjuvant Chemotherapy, Concurrent Chemoradiation, and Adjuvant Chemotherapy for High-Risk Extremity Soft Tissue Sarcoma

Elizabeth H. Baldini, MD, MPH, Axel Le Cesne, MD, and Jonathan C. Trent, MD, PhD

OVERVIEW

Standard treatment of large intermediate- and high-grade extremity soft tissue sarcoma (ESTS) typically includes wide excision and radiation therapy (RT).\(^1\,^2\) Randomized trials have confirmed the role of these two treatment modalities.\(^3\,^5\) Many patients do well with this approach, but for those with unfavorable features, risk for distant recurrence (DR) and, ultimately, mortality can exceed 50%. Unfortunately, universally accepted data elucidating effective treatments to prevent recurrences and improve survival for such high-risk patients are lacking. Accordingly, opinions about the appropriate role of systemic therapy for patients with high-risk localized ESTS vary. This article reviews the current literature pertaining to neoadjuvant chemotherapy, concurrent chemoradiation, and adjuvant chemotherapy for high-risk ESTS. All of these approaches are feasible and reasonable to consider. Ultimately, the decision to incorporate chemotherapy into the treatment regimen is best reached by discussion among an experienced multidisciplinary sarcoma team and should be tailored to the individual patient risk profile.

Standard treatment of intermediate and high-grade extremity soft tissue sarcoma (ESTS) includes wide excision and radiation therapy (RT).\(^1\,^2\) Randomized trials have confirmed the role of these two treatment modalities.\(^3\,^5\) Many patients do well with this approach, but for those with unfavorable features, risk for distant recurrence (DR) and, ultimately, mortality is approximately 50%.\(^6\) Thus, it is important to identify (1) which patients are at high risk for recurrence and (2) effective strategies to prevent such recurrences. Predictors for DR and mortality for ESTS have been consistently demonstrated to include high grade, large tumor size, and certain histologic subtypes.\(^7\,\^10\) For instance, a report of 1,091 patients showed 5-year overall survival (OS) rates of 52% for tumors larger than 15 cm.\(^10\) Callegaro and colleagues published nomograms to predict OS and disease-free survival (DFS) for ESTS; in addition to grade, size, and older age, adverse survival was demonstrated for vascular tumors, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor compared with all liposarcoma subtypes, myxofibrosarcoma, and undifferentiated pleomorphic sarcoma.\(^9\) Local control after wide excision and RT for ESTS is typically excellent (less than 15%), but reliable predictors for local recurrence (LR) include positive resection margins, presentation with locally recurrent disease, and older age.\(^7\,\^11\)

Unfortunately, definitive data from small single-arm or randomized trials elucidating effective treatments to prevent recurrences and improve survival for such high-risk patients are lacking. Although a meta-analysis by Pervaiz and colleagues that included individual patients from 18 randomized studies found a benefit in DFS and OS, these data have not been sufficient to result in a universal consensus.\(^12\) This is due in large part to the fact that ESTS is rare and consists of several diseases with different histologic subtypes, behaviors, and sensitivities to chemotherapy and RT. Accordingly, opinions about the appropriate role of systemic therapy for high-risk localized ESTS vary. This state is reflected in the National Comprehensive Cancer Network and European Society for Medical Oncology guidelines for ESTS, which both affirm that the data for systemic therapy are inconclusive and that its use for high-risk patients should be chosen on an individual basis.\(^1\,^2\) The lack of agreement on the potential role of systemic therapy for high-risk ESTS is further highlighted by the results of a recent survey performed among members of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group.\(^13\) Sarcoma experts from 12 centers and seven countries were polled regarding their practice patterns, and there was considerable heterogeneity in the use of pre- and postoperative chemotherapy, including the selection of agents administered.

This article reviews the current literature pertaining to neoadjuvant chemotherapy, concurrent chemoradiation (CRT), and adjuvant chemotherapy for high-risk ESTS.
NEOADJUVANT CHEMOTHERAPY

Although the data are limited, there is clinical rationale for neoadjuvant (preoperative or induction) chemotherapy. First, there is a long history of successful use of preoperative chemotherapy to induce tumor regression and facilitate limb- or organ-sparing surgery. Second, the use of preoperative chemotherapy allows earlier administration of chemotherapy to accelerate treatment of micrometastatic disease in patients at risk for metastases for whom adjuvant chemotherapy is possibly required. Third, neoadjuvant chemotherapy should be considered rather than adjuvant chemotherapy in situations where subsequent resection or radiation therapy may decrease tolerability of chemotherapy (e.g., nephrectomy, hepatectomy, wound healing). Last, the use of preoperative chemotherapy (two cycles over 6 weeks) in patients who have ESTS at high risk for metastatic progression allows identification of patients with chemotherapy-sensitive tumors (who radiographically respond to and stand to benefit from chemotherapy) from those whose tumors that harbor inherent primary chemotherapy resistance. Patients who develop metastatic disease while receiving preoperative chemotherapy are unlikely to benefit from an aggressive, potentially morbid, expensive surgery that, in the setting of widespread disease, could be viewed as unnecessary.

As indicated, multiagent chemotherapy anthracyclines plus ifosfamide at an adequate dose is the generally accepted treatment of choice in the neoadjuvant situation because higher response rates were observed in most randomized trials. Several single-center and multicenter phase II trials evaluated neoadjuvant chemotherapy combined with RT in series of up to 80 patients. These trials demonstrated the feasibility of this approach in studies performed at experienced sarcoma centers. However, in the absence of a control arm, the precise incremental effect of this strategy on limb salvage, progression-free survival (PFS) or OS could not be assessed. A randomized trial comparing low-dose neoadjuvant chemotherapy (doxorubicin at 50 mg/m² plus ifosfamide at 5 g/m²) followed by surgery compared with surgery alone included patients with grade I tumors as well as small tumors (< 5 cm). Although this study showed a trend in survival favoring chemotherapy (56% vs. 50%) it was not statistically significant.

A large, prospective trial compared three cycles of a conventional full-dose anthracycline (epirubicin at 120 mg/m²) plus ifosfamide (9 g/m²) combination (EI) to a histology-tailored chemotherapy in localized high-grade adult sarcoma of an extremity and trunk wall. This study included a homogeneous group of patients for whom adjuvant chemotherapy is generally administered: intermediate or high grade, tumor size greater than or equal to 5 cm, and ESTS or trunk wall soft tissue sarcoma (STS). The objective of this randomized trial was to reduce the risk for relapse with a histology-tailored chemotherapy regimen by 30% (high-grade myxoid liposarcoma with trabectedin at 1.3 mg/m²; leiomyosarcoma with gemcitabine at 1,800 mg/m² plus dacarbazine at 500 mg/m²; synovial sarcoma with high-dose ifosfamide at 14 g/m²; malignant peripheral nerve sheath tumor with etoposide at 150 mg/m² on days 1 to 3 plus ifosfamide at 9 g/m²; and undifferentiated pleomorphic sarcoma with gemcitabine at 900 mg/m² on days 1 and 8 plus docetaxel at 75 mg/m² on day 8). The histology-tailored regimens tested in the experimental arm were selected on the basis of the results observed when these regimens were used in the advanced setting over last two decades. After a median follow-up greater than 1 year, patients receiving neoadjuvant full-dose EI experienced a better DFS than patients treated with histology-tailored therapy. The projected DFS at nearly 4 years was 62% with the EI regimen versus 38% in the experimental arm (p = .004). Importantly, OS at 46 months was 89% in the standard chemotherapy arm and 64% in the histology-tailored chemotherapy group (p = .034). Adverse events were balanced between the two arms, with 114 adverse events in the histology-tailored arm and 125 events in the standard EI chemotherapy arm. After 70 events, the third interim analysis preplanned by the protocol led to suspended inclusion of new patients because of the favorable results of standard chemotherapy.

This study raises several questions. Are three cycles of histology-tailored chemotherapy sufficient (perhaps six to eight cycles would be more effective)? Are these histology-tailored agents less effective against microscopic disease or less cytotoxic than conventional chemotherapy? Are the histologic types chosen for histology-tailored therapy more prone to early recurrence? Should olaratumab be added to doxorubicin plus ifosfamide neoadjuvant therapy? Is there a role for “maintenance” adjuvant histology-tailored therapy after doxorubicin plus ifosfamide neoadjuvant therapy? Thus, three cycles of the histology-tailored therapy chosen in this study appear inadequate for the five histologic subtypes of localized STS.

PRACTICAL APPLICATIONS

- For some patients with high-risk extremity soft tissue sarcoma, the risk for distant recurrence and, ultimately, mortality can exceed 50%.
- Universally accepted data demonstrating the efficacy of systemic therapy to improve survival for these patients are lacking.
- Several reports of neoadjuvant chemotherapy, concurrent chemoradiation, and adjuvant chemotherapy have shown that incorporation of chemotherapy into the treatment regimen for high-risk patients with extremity soft tissue sarcoma is feasible.
- There is a strong rationale to consider using chemotherapy for such high-risk patients, but given the absence of universally accepted data, such decisions are best made on an individual basis and by experienced multimodality sarcoma treatment teams.
- Ongoing and future clinical trials will help identify the appropriate roles for chemotherapy in initial management of high-risk localized extremity soft tissue sarcoma.

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Achieving an R0 resection is the primary endpoint for sarcoma surgeons operating on a patient with a localized potentially curable STS. The R0 resection rate of 90% and the 4-year-PFS of 62% with E1 chemotherapy compares favorably to the outcome of patients operated upfront and receiving five cycles of adjuvant E1.20 In most published adjuvant series, the rate of R0 resection is approximately 50% with adjuvant chemotherapy never intended to rescue inadequate surgery. Therefore, increasing the rate of R0 resection with neo-adjuvant chemotherapy could positively affect outcome in localized operable high-grade ESTS and trunk wall STS.

The decision to use preoperative chemotherapy is generally reached at a multidisciplinary tumor board. Patients discussed in tumor boards before surgery in referral centers have significantly more adequate radiologic tumor assessments, more tumor biopsies, and a better adherence with clinical recommendations regarding the initial quality of surgery compared with patients who were not discussed at a multidisciplinary sarcoma tumor board.21 Participants in these tumor boards should discuss the decision to manage a high-risk STS with preoperative chemotherapy with an anthracycline plus ifosfamide in order to determine whether the patient would benefit from a smaller tumor, limb- or organ-sparing surgery, treatment of potential micrometastatic disease, and to determine the inherent chemosensitivity of an individual patient’s tumor. Ultimately, surgery remains the pillar of local control for localized STS.

NEOADJUVANT CHEMORADIATION

Neoadjuvant CRT is not standard of care, but national guidelines indicate it may be considered for high-risk patients with ESTS.2,22 The potential goals of concurrent or interdigitating chemotherapy and RT delivered before surgery could include (1) intensifying treatment to decrease LR for marginally resectable tumors or those felt to be at high risk for LR, (2) intensifying treatment to decrease DR and mortality, (3) de-intensifying RT to minimize wound complications, and (4) as a means of assessing treatment response to provide prognosis for outcome and help guide adjuvant treatments. Conclusive data on achievement of these goals are lacking, but several reports show that neoadjuvant CRT is feasible.

Interdigitated CRT (Conventional Dose, 50 Gy; Fraction Size, 2 Gy)

There are two experiences with an interdigitated CRT approach. The pilot study was conducted at Massachusetts General Hospital and consisted of three cycles of mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) with 44 Gy given as two split courses of 22 Gy (in 2-Gy fractions) in between chemotherapy cycles, followed by surgery and three cycles of postoperative chemotherapy with or without an additional 22 Gy.23 Results showed improved survival compared with historical controls. The Radiation Therapy Oncology Group (RTOG) subsequently enrolled 66 patients in RTOG 9514, a phase II trial with a very similar treatment approach, although the ifosfamide dose was higher.24 Efficacy was somewhat similar to that of the Massachusetts General study, but toxicities were greater, with 5% treatment-related deaths and 83% grade 4 toxicities rendering the scheme unacceptable. Longer-term follow-up showed a high 5-year LR rate of 22.2% but an encouraging 5-year survival estimate of 71.2%.24 A subsequent series from Massachusetts General of a more recent cohort of patients treated with the initial MAID regimen was associated with similarly favorable results.25 Although reported OS rates for these studies are promising, without well-matched comparison arms treated with RT alone, it is not possible to assess the efficacy of interdigitated CRT.

Concurrent CRT (Conventional Dose, 50 Gy; Fraction Size, 2 Gy)

The Mayo Clinic reported a preliminary experience for 39 patients treated with two cycles of ifosfamide, mitomycin, doxorubicin, and cisplatin (IMAP) followed by 45-Gy (1.8-Gy fractions) preoperative irradiation with concurrent reduced doses of MAP. An additional 10 to 20 Gy was delivered by intraoperative electrons, brachytherapy, or postoperative external-beam RT. The rate of grade 3 or greater hematologic toxicity was at least 77% and estimated 5-year OS was 80%.26 The Mayo Clinic in Arizona published a retrospective series of patients with stage II and III ESTS treated with surgery alone, neoadjuvant RT, or neoadjuvant CRT.27 Median RT dose was 50 Gy delivered with conventional 1.8- or 2-Gy fractions. The researchers found no difference between CRT and RT alone with respect to R0 resection rate, LR, DR, or OS. Toxicity was greater for CRT compared with RT. A more recent report from Palassini and colleagues describes the feasibility of neoadjuvant concurrent CRT in the setting of the combined Italian Sarcoma Group and Spanish Sarcoma Group randomized trial to compare full-dose epirubicin and ifosfamide for five cycles versus three cycles for high-risk localized STS of extremity and trunk.28 At the discretion of the treating physician, RT was delivered concurrently with cycles 2 and 3 to a dose of 44 to 50 Gy by using 2-Gy fraction sizes. The regimen of CRT was feasible and safe; delivered dose intensity was greater than 90%; however, grade 3 or 4 hematologic toxicity was common (61%), and there appeared to be an increase in wound complications with CRT (17%). Lastly, phase I studies have identified maximum tolerated doses of doxorubicin and gemcitabine delivered concurrently with 50 Gy of conventionally fractionated preoperative RT.28,29

Concurrent CRT (Hyperfractionation With Fraction Sizes of 3 to 3.5 Gy)

The most widely accepted neoadjuvant RT regimens use 2-Gy fractions sizes (to approximately 50 Gy); however, several investigators have explored CRT using larger fraction sizes of 3 or 3.5 Gy. Elber and colleagues at the University of California, Los Angeles have a long track record of successfully treating ESTS with hyperfractionated RT regimens using 3.5 Gy fraction sizes and concurrent chemotherapy. Since the 1970s, they have used five sequential concurrent CRT approaches, including, in chronologic order, the following:
ADJUVANT CHEMOTHERAPY

In contrast to osteosarcoma and Ewing sarcoma, for which perioperative chemotherapy is a required component of the standard of care, the use of adjuvant chemotherapy in the heterogeneous group of ESTS is not implemented universally. The combination of surgery and RT remains the cornerstone of local control for localized, resectable ESTS. Nevertheless, the strikingly high rate of local or distant relapse and ultimate mortality (approximately 50% for high-grade tumors) even after adequate local treatment of STS has inevitably sustained the clinical interest in using adjuvant chemotherapy to improve DFS and OS.

The most rigorous and important attempt to systematically analyze data on adjuvant chemotherapy for STS in the direction of overcoming the problem of inadequate power of small trials and minimizing potential biases was the Sarcoma Meta-Analysis Collaboration (SMAC) publication in 1997. This landmark report analyzing the outcome of more than 1,600 patients has become the reference publication on the subject and was the first meta-analysis of adjuvant chemotherapy for patients with sarcoma to date to be based on individual-patient data as opposed to small, single trials and retrospective analyses. The results of this meta-analysis provided statistically robust evidence that adjuvant chemotherapy significantly improved LR- and DR-free intervals. Moreover, the use of adjuvant chemotherapy defined a trend toward improvement in OS, although it was not statistically significant (hazard ratio, 0.89; p = .12). Importantly, the subset of extremity sarcomas (886) showed not only an absolute benefit in DFS but also an OS benefit of 7% at 10 years (hazard ratio, 0.80; p = .029).

After the publication of the SMAC meta-analysis, subsequent randomized trials were published in the field of adjuvant chemotherapy, all containing ifosfamide, larger average number of patients, and a greater proportion of STS with high risk for relapse. One of the largest positive trials was the Italian Randomized Cooperative Trial. The study involved a homogeneous cohort of 104 patients with high-grade extremity and girdle STS, with six cycles of adjuvant 120 mg/m² of epirubicin plus 9 g/m² of ifosfamide. At a median follow-up of 59 months, the study showed a statistically significant improvement in median relapse-free survival and OS, but it was not sustained at longer follow-up.

The most recent adjuvant chemotherapy trial, coordinated by the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group, is the largest conducted single study to date. This study involving 351 patients randomly assigned to no chemotherapy or adjuvant chemotherapy (five cycles of standard-dose doxorubicin at 75 mg/m² plus low-dose ifosfamide at 5 g/m²). The study demonstrated similar 5-year OS rates of 66.5% (chemotherapy) and 67.8% (control) between the two arms, perhaps due to the low dose of ifosfamide, 20% chemotherapy discontinuation rate, or the use of five instead of six cycles. Because of these differences, it is difficult to compare with other studies using standard, active doses of ifosfamide. Interestingly, the patients in whom R1 resection was performed were found to benefit from adjuvant chemotherapy with a 10-year OS of 44.7% compared with patients who did not receive chemotherapy, in whom survival was only 27.6%. It is important to stress that these subgroup and retrospective studies can be used only to generate hypothesis for future trials and cannot be used as evidence to propose recommendations for clinical practice in these selected subgroups.

In 2008, four additional trials were added to the individual-patient data from the meta-analysis performed in 1997. The addition of these trials increased the number of trials to 18, representing 1,953 patients to be included in the analysis. The odds ratio (OR) for local recurrence was 0.73 (95% CI, 0.56–0.94; p = .02) in favor of chemotherapy. Distant and overall recurrence were found to have an OR of 0.67 (95% CI, 0.56–0.82; p = .0001) in favor of chemotherapy. In terms of survival, single-agent doxorubicin had an OR of 0.84 (95% CI, 0.68–1.03; p = .09), which was not statistically significant. However, the OR for doxorubicin combined with ifosfamide was 0.56 (95% CI, 0.36–0.85; p = .01), strongly in favor of the
addition of chemotherapy to surgery and radiation in patients with localized STS. The updated meta-analysis underscores the efficacy of adjuvant chemotherapy in localized, resectable STS with respect to LR, DR, overall recurrence, and even OS. These benefits are enhanced with the addition of ifosfamide to doxorubicin-based regimens. However, the use of chemotherapy must always be weighed against side effects.

Therefore, there is an urgent need to determine whether a small subpopulation of patients absolutely do not benefit from adjuvant chemotherapy, such that these patients may be spared from the expense, side effects, and inconvenience of chemotherapy. Today, adjuvant chemotherapy may be proposed in specific situations after discussion at a multidisciplinary sarcoma tumor board. Adjuvant chemotherapy is generally proposed as an option to the high-risk individual patient for shared decision-making.

Our evidence-based insight into the effectiveness of systemic treatments for ESTS indicates that the decision should be individualized and treatment algorithms should incorporate available evidence regarding the use of adjuvant chemotherapy. The design of future adjuvant chemotherapy trials should incorporate novel agents with known activity in the metastatic setting.

New drugs, including novel molecularly driven agents, have been introduced in the treatment arena of mesenchymal tumors. Treatment decisions should be formulated according to the identification of patient subpopulations likely to benefit from adjuvant systemic chemotherapy, with consideration of specific tailored therapy for each histologic subgroup. Ultimately, and ideally, treatment planning should be based on LR and metastatic risk indices that incorporate such factors as quality of surgery, histologic features, molecular alterations or signatures, and other prognostic biomarkers yet to be identified and validated.

Future trials that could be considered include a randomized trial in selected groups of histologic subtypes with histology-tailored agents. Whether this would deliver results superior to those of the neoadjuvant study is unclear. Alternatively, one could use conventional chemotherapy (anthracycline plus ifosfamide) preoperatively for specific STS types, followed by postoperative histology-tailored therapy. Future ambitious adjuvant trials could be implemented in histologic subtypes of sarcoma in which a proof-of-concept efficacy has been observed in advanced diseases. Moreover, molecular profiling of tumors from patients with STS could lead to new actionable targets and potential adjuvant therapies even in the context of localized diseases. In this direction, the collection of fresh/frozen tissue and tumor imprints is encouraged because new molecular pathology assessments could be made at a later stage, in the patient’s interest.

Take-home messages for the use of adjuvant chemotherapy include the following: (1) adjuvant chemotherapy is reasonable for patients with a 5 cm or larger, intermediate- or high-grade STS, (2) adjuvant chemotherapy cannot rescue an inadequate initial surgery, (3) chemotherapy should contain adequate doses of an anthracycline (≥75 mg/m² of doxorubicin) and ifosfamide (≥9 g/m² per cycle) when possible, (4) clinical trials should continue to evaluate histology-tailored regimens, and (5) prognosis of patients with a localized STS starts at diagnosis and depends on quality management by an experienced multidisciplinary sarcoma team.

References


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Sarcomas are rare and heterogeneous tumors of mesenchymal origin, with a distinct age distribution, site of presentation, biologic behavior, and prognosis. There are more than 100 unique sarcoma subtypes, which arise from either the soft tissues or bones. Sarcomas account for 1% of adult and 15% of pediatric tumors, and they predominantly (80%) affect soft tissues, whereas only one-fifth affect the bones. Multidisciplinary approaches in the care of patients with sarcoma have led to great improvement in oncologic and functional outcomes. The prognoses of metastatic and refractory sarcomas, however, remain dismal: median survival is only 12 to 18 months.

Despite their rarity and heterogeneity, guidelines for the management of sarcomas have been developed in the United States (by the National Comprehensive Cancer Network) and Europe (by the European Society of Medical Oncology). Although these guidelines have been adapted broadly in the high-income countries, their applicability in lower-income countries remains limited, mainly because of resource constraints. Hence, there is an unmet need for recommendations specifically for these low-income areas that will be in accordance with the local availability of resources.

More than two-thirds of the world’s population live in low-income countries, which grapple with limited resources, fiscal deficiencies, and limited infrastructure, medical expertise, and technology. These geographic areas have seen a surge in cancer burden from a mere 15% in 1970 to 56% in 2008; by 2020, the estimated total number of new cancer occurrences will increase by 73% in low-income countries compared with a 29% increase in high-income countries.

Another striking difference is the cancer mortality to incidence ratio, which is 0.66 in low-income areas and almost double than the ratio in high-income countries (0.38). This discrepancy is probably caused by inequitable distribution as well as lack of health care access and expertise. Inadequately integrated or lack of established public health policies, cultural misbelief, and illiteracy lead to delayed presentation to medical attention, which adversely affects the rate of limb salvage and overall survival of patients with sarcoma. A multipronged approach is required to tackle these complex issues. Such enormous changes require a herculean effort, starting by accurate estimations of the sarcoma incidence; meticulous planning; formulation of strategies with short-, mid-, and long-term goals; and precise execution and follow-up. One approach will be to modify the best clinical practices to best possible evidence-based practices to suit the local needs. This article highlights modifications in the treatment and overall management of sarcomas in low-income countries.

THE CHALLENGE OF DIAGNOSING SARCOMAS AND OTHER RARE CANCERS IN LOW-INCOME COUNTRIES Biopsy and Tissue Processing

Biopsy is the most important step to establish an accurate diagnosis in sarcomas. With rare exceptions, histologic...
confirmation is essential before any treatment begins. Unplanned excision not only compromises the possibility for limb salvage procedures but also may adversely affect overall clinical outcomes. Ideally, biopsy should be performed at sarcoma treatment centers by the treating surgeon. In low-income countries, biopsies can be performed by a general surgeon or by an interventional radiologist in consultation with the treating surgeon.

An open incisional biopsy or a core needle biopsy can provide adequate tissue for diagnosis. A core needle biopsy is generally preferred, because it has the advantages of being an outpatient and cost-effective procedure, with a low complication rate and high accuracy in determination of the diagnosis. Usually, three to five cores are sufficient to provide adequate tissue for histopathologic diagnosis and additional molecular studies. An intra-operative image intensifier or ultrasound may be used in core needle biopsies to increase the diagnostic yield in challenging tumor locations. Unplanned open incisional biopsy is fraught with complication risks, such as higher infection rates, tumor seeding, and field contamination, and may compromise subsequent limb-sparing surgical options. Open biopsies require general anesthesia and hospitalization, which increase the overall cost. Fine-needle aspiration cytology is not recommended for initial diagnosis of sarcoma but can be done for confirmation of local recurrences or metastatic disease.

The most remarkable difference for the sarcoma pathologists who work in high-income medical institutions compared with low-income institutions resides in the limitless use of important ancillary tools, such as immunohistochemistry and molecular genetics. The state-of-the-art diagnosis of a sarcomatous growth, either soft tissue or bone, requires the appropriate and careful use of immunohistochemistry and molecular genetic techniques.

The use of immunohistochemistry is sine qua non for a correct and unquestionable diagnosis of most mesenchymal neoplasms. The appropriate use of immunohistochemical markers, although necessary, relies on careful interpretation in context with the morphologic aspects of the neoplasm in question. The sensitivity and specificity of the antibodies used, should always be taken into account. Probably the best example of this divergence between sensitivity and specificity is observed with CD99, an antibody that is extremely sensitive but not as specific for Ewing sarcoma/primitive neuroectodermal tumor (PNET), which is expressed in a variety of neoplastic cell types, such as poorly differentiated round-cell type synovial sarcoma, alveolar rhabdomyosarcoma, T-cell lymphoma, and mesenchymal chondrosarcoma. This divergence between sensitivity and specificity obliges the use of a panel of antibodies to overcome this challenge and to reach the most precise diagnosis. A recommended list of the minimum immunostains that should be used in low-income settings is listed in Table 1.

The use of molecular genetic techniques, such as fluorescence in-situ hybridization or reverse transcriptase polymerase chain reaction, is applied frequently in the diagnostic workup of sarcomas. The introduction of genetics in the daily diagnostic practice of sarcomas affected the pathogenesis studies of sarcomas, the development of newer classification systems, and the prognostication of some sarcomatous entities.

### TABLE 1. The Minimum List of Immunostains That Should Be Used in Income-Constrained Settings

<table>
<thead>
<tr>
<th>Immunostain</th>
<th>Differentiation</th>
<th>Neoplasm</th>
</tr>
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<tbody>
<tr>
<td>AE1/AE3, CAM5.2, EMA</td>
<td>Epithelial</td>
<td>Carcinomas, myoepithelioma, synovial sarcoma, epithelioid sarcoma</td>
</tr>
<tr>
<td>S-100 protein</td>
<td>Melanocytic, neural</td>
<td>Melanomas, peripheral nerve sheath tumors, clear cell sarcoma</td>
</tr>
<tr>
<td>HMB-45, Melan-A</td>
<td>Melanocytic, perivascular epithelioid cytology</td>
<td>Melanomas, clear cell sarcoma, pecomas</td>
</tr>
<tr>
<td>Smooth muscle actin</td>
<td>Smooth muscle, myofibroblastic</td>
<td>Smooth muscle and myofibroblastic neoplasms</td>
</tr>
<tr>
<td>Desmin</td>
<td>Smooth and skeletal muscle</td>
<td>Smooth muscle and skeletal muscle neoplasms</td>
</tr>
<tr>
<td>Myogenin, MyoD1</td>
<td>Rhabdomyoblastic</td>
<td>Rhabdomyosarcomas</td>
</tr>
<tr>
<td>CD34</td>
<td>A few fibroblastic lesions</td>
<td>Solitary fibrous tumors, dermatofibrosarcoma protuberans</td>
</tr>
<tr>
<td>CD31</td>
<td>Endothelial</td>
<td>Benign and malignant vascular neoplasms</td>
</tr>
<tr>
<td>CD99</td>
<td>Poor specificity</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>CD45, CD20, CD3</td>
<td>Lymphoid</td>
<td>Lymphoproliferative lesions</td>
</tr>
</tbody>
</table>

Abbreviation: PNET, primitive neuroectodermal tumor.
Molecular genetics have been extremely useful in the daily routine practice of resourceful pathology laboratories, and fluorescence in-situ hybridization has been more effective than reverse transcriptase polymerase chain reaction-based techniques. Like the results from immunohistochemistry, the results derived from molecular genetic techniques should be interpreted carefully in the context of the morphologic features of a given neoplastic entity.

**Pathologist Expertise**

Bone and soft tissue pathology is perhaps the subspecialty that has the greatest overlap with other pathology subspecialties. Mesenchymal non-neoplastic and neoplastic growths can occur primarily in somatic, retroperitoneal, and mediastinal soft tissues; inside mesothelial-lined cavities; and in visceral parenchyma. Like nonmesenchymal neoplasms, such as carcinomas, melanocytic lesions, lymphoproliferative growths, and germ cell neoplasms, sarcomas can primarily or secondarily involve somatic soft tissues. Bone and soft tissue sarcoma pathologists should also be experts in general surgical pathology to recognize the occurrence of such nonmesenchymal lesions that involve somatic soft tissues.

In addition, any pathologist who works in a low-income setting must be familiar with the latest literature in diagnostic pathology of bone and soft tissue neoplasms and should display good judgment when more sophisticated ancillary techniques are necessary to exclude an important differential diagnosis. Cooperation with tertiary and more equipped medical institutions should be sought when limitations in pathology resources exist and prohibit conclusive diagnosis. Country-specific databases of physicians specialized in sarcomas and other rare tumors can also be created and become publicly available in an effort to facilitate second opinion referrals from low-income countries.

**Gross and Histologic Examination**

Although most specimens currently submitted for diagnosis of possible sarcomas are small fragments of tissue, pathology laboratories occasionally receive large specimens and whole organs for examination. When whole organs are delivered, a careful gross examination of the specimen is necessary to confirm the diagnosis of sarcoma.

After the gross examination, a careful histologic examination, starting with the determination of the neoplastic growth pattern, should take place. Table 2 shows the main growth patterns of sarcomatous growth and the associations between growth patterns and histologic types of neoplasms. Other histologic features to be considered during the histologic examination of a sarcoma are the presence and type of necrosis, the presence of calcifications, and the degree and type of intercellular stroma and matrix formation.

**Diagnostic Approach**

The diagnostic workup in low-income countries should be well supported by accurate clinical information as well as by laboratory and imaging tests. Sarcomas tend to follow specific patterns of age and sex distribution. Although exceptions occur, tumors such as neuroblastomas and botryoid and spindle cell variants of embryonal rhabdomyosarcomas affect infants and toddlers more frequently, whereas Ewing sarcoma/PNET, alveolar rhabdomyosarcoma, synovial sarcoma, mesenchymal chondrosarcoma, and epithelioid sarcoma tend to affect older children, adolescents, and young adults. Mesenchymal growths frequently affect both sexes; however, a tendency of leiomyosarcomas to affect women and a tendency of desmoplastic small round cell tumors (DSRCTs) to occur most frequently in young men are well demonstrated in the literature.

Another important feature of sarcomas that can assist in diagnosis is the location of the primary lesion. For example, synovial sarcoma, mesenchymal chondrosarcoma, and alveolar rhabdomyosarcoma occur more often in deep soft tissues of extremities. In contrast, DSRCTs involve serosal surfaces, mainly the peritoneum, and well-differentiated and dedifferentiated liposarcomas are predominantly seen in retroperitoneum. The breast parenchyma is a frequent location as well, either for primary or metastatic involvement, of alveolar rhabdomyosarcoma that affects young women.

Although hematogenous spread is the most common pattern of sarcoma metastatic spread, other more unusual patterns of distant metastasis can assist in the identification of some mesenchymal neoplasms. Lymphatic spread sometimes can be observed in Ewing sarcoma/PNET,

### TABLE 2. Main Growth Patterns Presented by Sarcomatous Growth

<table>
<thead>
<tr>
<th>Growth Pattern</th>
<th>Type of Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse</td>
<td>Lymphomas, Ewing sarcoma/PNET, mesenchymal chondrosarcoma</td>
</tr>
<tr>
<td>Cord-like with fibrosis</td>
<td>Ewing sarcoma/PNET</td>
</tr>
<tr>
<td>Nesting</td>
<td>Neuroblastoma, DSRCT</td>
</tr>
<tr>
<td>Staghorn</td>
<td>Synovial sarcoma, mesenchymal chondrosarcoma</td>
</tr>
<tr>
<td>Alveolar</td>
<td>Synovial sarcoma, mesenchymal chondrosarcoma, embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Spindle/fascicular</td>
<td>Synovial sarcoma, mesenchymal chondrosarcoma, embryonal rhabdomyosarcoma</td>
</tr>
<tr>
<td>Biphasic</td>
<td>Synovial sarcoma, malignant peripheral nerve sheath tumor, mesenchymal chondrosarcoma</td>
</tr>
</tbody>
</table>

Abbreviations: DSRCT, desmoplastic small round cell tumor; PNET, primitive neuroectodermal tumor.
rhabdomyosarcomas, and neuroblastoma. Neuroblastoma is responsible for widespread metastatic disease that involves bone marrow, lymph nodes, liver, orbital area, and bone. A leukemic picture can be associated with alveolar rhabdomyosarcoma in instances of occult clinical presentation with early metastatic involvement of bone marrow. Metastatic deposits in lung and brain parenchyma can be the first clinical presentation of an occult alveolar soft part sarcoma.

Imaging studies are invaluable in the diagnostic workup of malignant bone and soft tissue neoplasms. Conventional radiography (in two perpendicular planes) should be the first investigation, because it allows assessment of size, location, margination, internal matrix, periosteal reaction, and presence of pathologic fracture. Cross-sectional imaging of the primary site (by CT/MRI) should include the entire anatomic area to detect any regional metastases or satellite lesions. MRI is the investigation of choice for local staging in extremity sarcomas, whereas CT scan is more helpful in retroperitoneal sarcomas. These investigations should be performed before tissue biopsy for histopathologic confirmation. Lung is the most common site of metastasis; therefore, baseline imaging of the chest (CT scan or chest x-ray) is required in most cases. CT scan of the chest is recommended by most of the guidelines on the basis of its high sensitivity (100%) and specificity (99.6%).

Radionuclide bone scan with technetium should be obtained at baseline to assess skeletal disease in bone sarcomas. The role of PET/CT in bone sarcomas and soft tissue sarcomas is evolving, but PET/CT has not been proven superior to bone scan and chest CT scan in the detection of bone or lung metastasis, respectively. Discovery of an additional site of metastasis with PET scan may not change the clinical course or eventual outcome. Because it is not widely available in low-income countries and is quite costly, PET/CT is not recommended in low-income settings. A non-contrast CT scan of the chest with contrast MRI of the primary anatomic location of high-grade soft tissue sarcoma and an additional bone scan in bone sarcomas can be the recommended initial staging protocol in low-income countries.

TREATING SARCOMAS AND OTHER RARE CANCERS IN RESOURCE-CONSTRAINED SETTINGS

Management of sarcomas has changed dramatically during the past five decades, as evidenced by improvement in outcomes: 5-year survival has increased from 20% to 70%, and the feasibility of limb salvage procedures has increased in 90% of patients with sarcoma. These advances were achieved because of multiantigen chemotherapy regimens, development of imaging and diagnostic modalities, and refinements of surgical training and equipment.

Ideally, sarcomas should be treated in established sarcoma treatment centers that have experience with at least 50 patient cases of sarcoma per year. These centers usually have multidisciplinary teams that comprise a variety of experts (oncologic surgery, medical oncology, radiation oncology, sarcoma pathology, and musculoskeletal radiology) and that are supported by rehabilitation, palliative care services, and adequate infrastructure to execute complex treatment regimens.

A clinician with basic oncology training can guide evaluation, radiologic investigations, and biopsy in low-income countries. The fundamental requirement to initiate treatment must include the availability of adequately trained surgeon, medical oncologist, and radiation oncologist. A team must discuss patient cases to finalize the treatment plan, because multidisciplinary teams have been shown to improve patient outcomes. Medical centers should either provide in-house adequate infrastructure in terms of well-equipped operating rooms, intensive care units, blood banks, and radiotherapy units (cobalt units or linear accelerator) or should have these services available in the vicinity. Additional support may be sought from regional and tertiary referral centers.

Surgery

Complete surgical resection remains the gold standard for local control of sarcomas. Surgery aims to achieve complete tumor removal and provide a durable, cosmetically and functionally reconstruction with the least short- and long-term complications. The barrier concept of surgical margins was introduced by Kawaguchi et al, who emphasized the quality of surgical resection margins. Barrier referred to any tissue with resistance to tumor invasion and was converted to thickness of normal tissue. Thick barrier was defined as 3 cm thickness of normal tissue, thin barrier as 2 cm, and join cartilage as 5 cm. Thus, the extent of resection has moved away from amputations or overly morbid operations toward limb-sparing procedures and increasingly has become histology specific.

General surgeons can perform superficial soft tissue sarcoma excisions and amputations, and trained orthopedic oncologists are required to perform a bone sarcoma resection and reconstruction. Complex sarcoma surgeries require special expertise and additional support from other subspecialties, like plastic, vascular, colorectal, and urology surgeries. If adequate expertise or infrastructure are not available, amputation may be considered, because complete disease removal is essential for long-term survival. Reconstruction of post-tumor resection defects remains a challenge. Mega-prosthesis is one of the most commonly used modalities to reconstruct these defects. The cost may be a hindering factor, so development of locally manufactured mega-prosthesis should be the focus in low-income settings. If a mega-prosthesis is unavailable, arthrodesis with nail cement spacers can provide an alternate option. The structural defects in a growing skeleton are best reconstructed with an expendable prosthesis, but the high cost of these implants may not permit their use in the majority of patients in low-income countries. In such situations,
tumor sizes typically are more than 5 cm, are high-grade

An adolescent patient (nearing skeletal maturity) can be treated with an intraoperative limb lengthening procedure on the affected side, which gets compensated as the patient grows, so it may circumvent the need for an expandable mega-prosthesis. Cost-effective reconstructions like nail cement spacers or plate spacers, used specifically in proximal humeral and intercalary resections, have functional outcomes equivalent to more expensive prosthetic reconstructions.

Biologic reconstructions are financially feasible and durable options for limb salvage procedures. The buddy bone reconstructions, like an ulna translocation for distal radius tumors and the tibia-profibula procedure for tibial diaphyseal and distal tibial tumors, are examples of reconstruction by an adjacent pedicle bone. These procedures do not require additional plastic and microvascular surgeries, so they are well suited for low-income countries.

Reconstruction of intercalary defects can be done with various nonbiologic (e.g., prosthesis, nail cement spacers) or biologic (e.g., allograft, autografts, or sterilized tumor autograft bone) methods. Sterilization of tumor-bearing bone can be done by numerous methods (e.g., radiation, pasteurization, autoclaving, liquid nitrogen), but extracorporeal irradiation and re-implantation is the most common method used. This method is cost-effective, averts the need of expensive custom-made implants, and can be performed at centers with limited resources. Long-term results have repeatedly shown good functional and radiographic outcomes of this technique.

Another challenge in sarcoma surgery is the variety of sacro-pelvic resections, which are complex surgeries and which should only be performed at specialized centers. These procedures are associated with high rates of intraoperative (i.e., massive blood loss, vascular, nerve and visceral injuries, positive surgical margins) and postoperative (i.e., wound dehiscence, flap necrosis, and infection) complications. Prosthetic reconstruction of pelvic defects requires an expensive prosthesis and is associated with high rates of complications and revision surgeries. In low-income countries, pelvic defects should be treated with minimal or no reconstructions. Mesh-plasty for partial acetabular defects or complete hemipelvic resections provides reasonable functional outcomes with fewer complications and low rates of re-resections.

Chemotherapy

Systemic chemotherapy is used for the treatment of sarcomas in both palliative and curative settings. Most patients with sarcoma will die as a result of metastatic disease, so the identification of a high-risk group of patients—in which tumor sizes typically are more than 5 cm, are high-grade tumors, are deep to fascia location, and have specific histologies and sensitivity to chemotherapy—has led to incorporation of adjuvant therapy to eradicate micrometastasis early. Anthracycline-based regimens have been the standard of care for the past four decades for most histologic subtypes of sarcomas. Most of the chemotherapy agents used in sarcomas either in first or subsequent lines, such as doxorubicin, ifosfamide, gemcitabine, vincristine, cisplatin, etoposide, and docetaxel, were recently included in the 20th edition of WHO Essential Medicines List published in 2017.

Radiotherapy

Amputation was the standard of care in the management of sarcomas until the landmark study by Memorial Sloan Kettering Cancer Center showed comparable disease-free survival and overall survival in patients who underwent amputation or limb-sparing surgery followed by adjuvant radiation, despite an increase in local recurrence in the limb-sparing surgery group. Two subsequent prospective trials also highlighted the benefit of adjuvant radiation (external-beam radiotherapy and brachytherapy) in soft tissue sarcomas for local control but failed to demonstrate a survival benefit.

Radiation therapy can be administered in the adjuvant or neoadjuvant setting, and the risks and benefits in both settings were compared in a randomized trial. The two study groups had equivalent rates of local recurrence at 3.3 years of follow-up. Wound complications were more frequent in preoperative radiotherapy arm, whereas joint fibrosis and edema were significantly higher in the postoperative radiotherapy arm. Adjuvant radiotherapy may be preferred in low-income countries, because it obviates or reduces the need for additional plastic surgery procedures. Cobalt units or linear accelerators can deliver radiotherapy. Linear accelerator is preferred for dosimetric reasons, but cobalt units are preferable because of their low cost, ease of use, and low delivery requirements. To aid patient selection for adjuvant radiation therapy, a predictive nomogram is available to assess the risk of local recurrence in individual patients treated with surgery alone on the basis of five factors: age older than 50 years, high-grade histology, tumor size greater than 5 cm, close or positive margins, and specific histology.

Also, radiation therapy helps provide reasonable local control in Ewing sarcoma as a definitive therapy in lieu of surgery in select patients in whom wide surgical resection is not feasible or leads to high morbidity (e.g., axial tumors). Newer methods of radiotherapy delivery by image guidance (i.e., intensity-modulated radiation therapy) or proton-beam therapy are associated with reduced toxicities and with similar oncologic outcomes compared with conventional radiotherapy. However, these newer methods lead to
high treatment costs and so are not advocated for low-income countries.67

Rehabilitation
Rehabilitation plays a key role in improvement of the functional outcomes and quality of life of patients with sarcoma after extremity tumor resection (limb salvage/amputation). Protocols must be individualized on the basis of the type of surgery and reconstruction methods with an aim to achieve early independent mobilization. The requirement of additional orthosis or external prosthesis must be addressed during recovery. A set of instructions with pictorial diagrams can serve as a reference for local therapists and can be used to continue rehabilitation in remote areas.68 These patients can be consulted by telephone and should be assessed periodically during their oncologic follow-up visits, or earlier if deemed necessary.

Surveillance
Upon completion of multimodal treatment, surveillance to detect local recurrence or metastasis begins by monitoring and analyzing functional and oncologic outcomes as well as treatment-related toxicities. In the initial post-treatment setting, most of the current practices follow a more frequent (every 3 months) imaging schedule, which, however, lacks robust clinical evidence.69,70 A less intense surveillance protocol is associated with fear of late diagnosis of relapses, and a more intensive one is associated with high cost and increased anxiety for the patient and family. A phase III noninferiority, randomized, controlled trial showed that a cost-effective (chest radiograph and clinical examination) every-6-months protocol is not inferior to an imaging-intensive every-3-months protocol in terms of overall survival in high-grade sarcomas. Until more evidence emerges, this less intense surveillance protocol may be adapted, especially in low-income settings.71

ACCESS TO NEW AND EXPENSIVE MEDICATIONS IN LOW-INCOME COUNTRIES
The development of newer treatments in sarcomas compared with other solid tumors had been limited in the past 2 decades, with the exception perhaps of imatinib and other tyrosine kinase inhibitors in G1 stromal tumors. During the past 3 years, three new medications were approved in the United States for metastatic sarcomas: pazopanib, trabectedin, and olaratumab. However, the cost of innovation drives the high medication prices worldwide, which often prohibits their use in low-income countries. There have been estimates that the cost of research and development of a new drug can range from $320.0 million to as high as $2.7 billion.72,73 A more recent analysis estimated that the cost to develop a cancer drug was $648.0 million, with a median development time of 7.3 years.74 After a drug is approved, the revenue it generates also can range widely, from $204.1 million to $22 billion. With a mean length of market exclusivity of 14 years,75 it is likely that these revenues will continue to increase. As such, the cost of cancer medications, especially for new therapies, ranges from $6,000 to $13,000 per month of treatment in the United States.76 In addition to high medication prices, the costs associated with the administration of intravenous chemotherapy and the supportive care they require also are contributing factors to the lack of access to cancer medications in low-income countries. In a retrospective study of patients with metastatic sarcoma, the costs associated with the administration of chemotherapy accounted for up to 16.5% of the costs per treatment visit in the United States.77 In view of the unmet needs for effective sarcoma treatments, however, newer medications, albeit at high cost, are used in most high-income countries with variations mainly in the sequence that they are offered to the patients: after or before the most common chemotherapy doublet, doxorubicin and ifosfamide.

Low-income countries often manage to circumvent patents and manufacture medications locally, through compulsory license for treatments on the grounds of public interest, which lowers the costs and, ultimately, prices compared with those in the high-income countries. This concept of mandatory licensing, though, does not come short of controversy. From public and global health standpoints, substitution of patented drugs with generics is cost-effective and can increase access to essential and life-prolonging medications in low-income countries. The counter argument expressed by critics, although not necessarily supported by evidence, is that this failure to protect intellectual property worldwide can eventually lead to a lack of incentives for innovation and fewer new medications.78

Even in patented drugs though, there is a wide price variation globally. Prices are more affordable prices in the low-income countries, but this affordability is not translated to greater patient access in these countries.79 When affordability is measured by the percentage of per capita gross domestic product (GDP) required to pay for a month’s supply of medication, patients in the United States or Australia, for example, are more likely to obtain those medications despite the higher prices. In contrast, patients in countries like India, where the medications have lower prices, are still not able to afford them because of a much lower GDP and a higher price-to-GDP ratio.79

What can be done to improve access in low-income countries, where cost is the main factor that hinders medication access? Despite controversy, compulsory licensing does offer an alternative to the high costs of developing a drug in low-income countries. In addition, direct negotiations with pharmaceutical companies can lead to successful results, because more companies now fund international prescription assistance programs. Tiered pricing, in which medications can be sold at lower prices in emerging economies as long as the cost of production is covered, is an alternative that is supported by economics principles and industry. Although less applicable in the treatment of sarcoma, at least at the present time, biosimilars are an alternative to biologic agents at a lower cost. A number of biosimilars have already been approved in the United States, in Europe, and in many other countries. Approvals notwithstanding, development
of and applications for biosimilars remain challenging, because biosimilars are not generics of branded drugs, so their efficacy must be shown in clinical trials before marketing.80

If health policies and systems are established, adoption of universal insurance coverage in low-income countries also can ensure adequate access to health care and new medications. Nonetheless, the majority of the low-income world still struggles to apply basic health insurance coverage, let alone coverage of the comprehensive care required by patients with cancer.81 Other ways to improve access can include the promotion of drug development in emerging markets and more involvement in clinical trials in the low-income setting, as long as challenges such as ethical matters of informed consent process, potential conflict of interests, and participant financial compensation are addressed via regulatory agencies.81

**FUTURE PERSPECTIVES**

Modification of treatment guidelines may not be adequate to achieve the desired goals in the treatment of patients with sarcoma. We must follow an integrated approach that involves physicians, educational bodies, industry, and government policy makers.

National and state registries can give an exact account of the number of sarcoma patient cases and will help plan equitable distribution of health care services. Public education and awareness for seeking early and correct medical care should be advocated, too. Patients whose cases that require more expertise should be referred to a sarcoma treatment center for better outcomes. This can be emphasized by a well-structured medical education program or by legal enforcements.

National sarcoma education societies can help propagate education. Formulation of sarcoma management guidelines (modified for each low-income setting) can act as the reference and benchmark for all sarcoma-treating physicians and can help improve the overall standards of sarcoma care.

In low-income countries, the majority of treatment costs are bared by patients rather than by insurance or public health care initiatives. Technology can be used to provide solutions customized to local needs, to craft an affordable and accessible sarcoma health care system.

National and international collaborations will not only provide the opportunity for enhancement of medical education and training but also help share current information, technologies, and ideas to bridge the gap between bench to bedside. Comprehensive clinical and cancer tissue databases from these centers can be the nidus of major clinical and basic science research.

**References**


Sarcomas are a diverse group of cancers with mesenchymal origin. Although sarcomas comprise less than 1% of cancers, there are more than 50 different subtypes that are quite different from one another in terms of both their biology and clinical behavior. Historically, the need for adequate patient numbers in clinical trials has pushed sarcoma researchers to lump these very different malignancies together and treat the patients using a “one-size-fits-all” approach. However, with improvements in our scientific understanding, we are finally ready for a histology-tailored therapeutic approach to these complex diseases. In this review, we discuss key advances in our understanding of the biology underlying selected sarcoma subtypes and how targeting these subtypes is relevant therapeutically with respect to both molecularly targeted agents as well as immunotherapy.

Soft tissue sarcoma (STS) constitutes a group of more than 50 different subtypes of rare mesenchymal tumors comprising less than 1% of adult cancers. Despite the heterogeneous nature of the STS family of tumors, the “one-size-fits-all” approach dominated STS therapy for more than 30 years. It originated from the need to lump together patients with STS for the sake of rapid accrual in clinical trials. Those trials were underpowered to detect any advantage for one particular subgroup over the other (as such, an advantage would have been diluted within the entire population). Additionally, uncommon sarcoma subtypes were under-represented in those trials, rendering it almost impossible to draw conclusions on a possible benefit in a rare histologic subtype. The one-size-fits-all approach led to the use of anthracyclines alone (e.g., doxorubicin) or in combination with alkylating agents (e.g., ifosfamide) as the dominant form of STS treatment for the past 3 decades, with other more contemporary regimens such as gemcitabine in combination with docetaxel or dacarbazine to follow. Although these regimens have been broadly used, the benefit from treatment in different STS subtypes varies. For example, the combination of doxorubicin with ifosfamide is shown to be highly active in myxoid liposarcoma (MLPS), whereas it is inactive in clear cell sarcomas. The combination of gemcitabine with docetaxel is active in leiomyosarcoma with no benefit in MLPS.

On the same note, angiogenesis, through activation of VEGF receptors VEGFR-1 to VEGFR-3, platelet-derived growth factor receptors PDGFRα and PDGFRβ, and other targets, is a common pathway of disease progression in certain STS subtypes. Antiangiogenic drugs such as pazopanib or sunitinib have shown activity in many common subtypes, such as leiomyosarcoma and synovial sarcoma, but not in lipomatous tumors. Interestingly, they have activity in a number of rare STS subtypes with relative resistance to chemotherapy, such as alveolar soft-part sarcoma (ASPS) or solitary fibrous tumors (SFTs).

Clearly some STS subtypes are more responsive to certain therapies than others. The differential response to cytotoxic agents stems from mechanisms of oncogenesis and progression diverse for each histotype. Currently, much of our knowledge regarding the responsiveness to therapy of individual STS subtypes is a matter of long-standing acquired clinical experience rather than a mechanistic biologic understanding, although this is changing as we continue to learn more.

One problem with subtype-specific therapy is that historically there has been disagreement among pathologists regarding diagnoses. Here again, a better understanding of the oncogenetic pathways provides an opportunity of reaching a clear, objective, and universally agreed-upon diagnosis of an STS subtype for a given patient. Although morphology and immunohistochemistry are still the first step toward any diagnosis, ancillary molecular diagnostics, such as molecular cytogenetics and reverse transcription–polymerase chain reaction, are becoming more critical. Molecular diagnostics have enriched our understanding of the complex genetic landscape of STS and laid the
infrastructure for a precision approach to therapy. Currently, driver mutations that potentially induce oncogenesis have been identified in almost one-third of STS subtypes; for example, well-differentiated liposarcoma (WDLPS) and dediffereniated (DDLPS) are characterized by amplification of \( MDM2 \) and \( CDK4 \) genes.\(^{13,14}\) There is overexpression of the hepatocyte growth factor receptor (MET) in clear cell sarcoma.\(^7\) Anaplastic lymphoma kinase (ALK) gene rearrangement with multiple partners can be found in 50% of cases of inflammatory myofibroblastic tumors (IMTs),\(^{15}\) whereas disruption of the mTOR signaling pathway often as a result of mutations in the \( TSC1 \) and \( TSC2 \) genes is evident in perivascular epithelioid cell tumors (PEComas).\(^{16}\) Furthermore, these efforts have also revealed promising targets that, although not related to oncogenesis, may be useful therapeutically; for example, high expression of NY-ESO-1 in synovial sarcoma and MLPS has been used as an immunotarget of immunotherapy.\(^{17,18}\)

In this overview, we use a histology-driven approach to describe the utility and activity of chemotherapeutics, targeted agents, and immunotherapies based on the mechanism of action and target expression in selected STS subtypes. For convenience purposes, this article is divided into two parts: the first part focuses on conventional treatments including chemotherapy and targeted therapies, and the second part focuses on immunotherapy.

### HISTOLOGY-DRIVEN TREATMENTS: SUBTYPES WHERE CHEMOTHERAPY IS MOST ACTIVE Synovial Sarcoma

Synovial sarcoma is an STS of uncertain differentiation. The karyotypic hallmark of synovial sarcoma is the \( t(X;18) \) (p11.2;q11.2) translocation, involving the \( SS18 \) gene and one of several \( SSX \) genes (usually \( SSX1 \) or \( SSX2 \)).\(^3\)

Conventional chemotherapy with anthracyclines and/or ifosfamide, trabectedin, or pazopanib can be quite effective temporarily for patients with synovial sarcoma\(^9,19-21\) and is considered the standard of care. Several other targeted treatments have been used, with partial response reported with sorafenib,\(^{22}\) cediranib,\(^{23}\) and cixutumumab\(^{24}\) monotherapy (Table 1), but none have been approved for synovial sarcoma treatment to date.

Increased understanding of the oncogenic role of \( SS18:SSX \) translocation in the process of synovial sarcoma progression led to advances in the development of biology-driven therapies. For example, the \( SS18:SSX \) translocation translates into a fusion protein that alters chromatin remodeling by altering switch (SWI)/sucrose nonfermentable (SNF) also known as BAF (BRG1- or HBRM-associated factors). The native \( SS18 \) protein is one of many protein components of the multiprotein SWI/SNF complex, located adjacent to the SMARCB1/INI1 protein. Alteration in SWI/SNF complex function has been suggested to induce tumorigenesis through altered epigenetic regulation of gene transcription.\(^{31}\) The fusion protein dislocates both the native \( SS18 \) and SMARCB1/INI1 from their natural positions, induces degradation of SMARCB1/INI1 protein, and disrupts the complex function, redirecting it to target the promotor region of sex-determining region Y-box 2 (Sox2). The binding of the altered SWI/SNF complex to the Sox2 promotor displaces the enhancer of zeste homolog 2 (EZH2) and induces Sox2 activation, a stage necessary for synovial sarcoma proliferation.\(^ {32}\) In vitro, the oncogenic Sox2 overexpression induced by the altered SWI/SNF complex is not affected by EZH2 inhibition by tazemetostat.\(^ {31}\) The incomplete suppression of tumorigenesis in synovial sarcoma cells may in part explain why treatment with tazemetostat, a potent and selective EZH2 inhibitor, has been limited. Tazemetostat was tested in a phase II multiarm study that included 33 patients with SS18 rearrangement-positive pretreated synovial sarcoma. Despite the robust rationale for using an EZH2 inhibitor in SS18-positive synovial sarcoma, no objective responses were detected. Stable disease as the best response was observed for 11 patients (33%), and five patients (15%) had stable disease that lasted for 16 weeks or longer.\(^ {33}\) The role of immunotherapy in synovial sarcoma is discussed in detail in the section on immunotherapy.

### Myxoid/Round Cell Liposarcoma

MLPS is an adipocytic tumor composed of round-shaped primitive mesenchymal cells and lipoblasts within a myxoid stroma with predilection in the deep soft tissues of the extremities.\(^1\) Compared with other STS subtypes, MLPS has a strong predisposition to metastasize to nonpulmonary sites.
<table>
<thead>
<tr>
<th>Agent</th>
<th>Targets</th>
<th>Study Design</th>
<th>SS Results</th>
<th>Patients With SS, n</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Raf-1, PDGFR-b, VEGFR-2/3, FLT3, KIT</td>
<td>Phase II; 122 patients with recurrent or metastatic sarcoma received 400 mg of sorafenib twice daily</td>
<td>6 patients with SD; 3-month PFS, 42%</td>
<td>12</td>
<td>Maki et al (2009)</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Raf-1, PDGFR-b, VEGFR-2/3, FLT3, KIT</td>
<td>Phase II; 100 patients with advanced STS pretreated with doxorubicin received 400 mg of sorafenib twice daily</td>
<td>2 patients with a PR</td>
<td>7</td>
<td>Santoro et al (2013)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR-1–3, PDGFR-a/b, c-KIT</td>
<td>Phase II; 142 patients with intermediate, high-grade advanced STS second or third line, received 800 mg of pazopanib daily; patients were stratified to adipocytic STS, leiomyosarcoma, SS, and all others</td>
<td>18 patients with SS (49%) achieved the primary endpoint of PFS rate at 12 weeks; 5 had a PR, 4 of which had responses that lasted 415 to 812 days</td>
<td>37</td>
<td>Sleijfer et al (2009)</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>VEGFR-1–3, PDGFR-a/b, c-KIT</td>
<td>Phase III; 369 patients with metastatic STS (no adipocytic included) in second line and beyond were randomly assigned to placebo or 800 mg of pazopanib daily (PALETTE)</td>
<td>Patients with SS showed a PFS rate not statistically different from the other histotypes (HR 0.82 for SS vs. other sarcoma; 0.51–1.32)</td>
<td>NA</td>
<td>van der Graaf et al (2012)</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>VEGFR-1–3, PDGFR-a/b, KIT, FLT3, RET, and CSF-1</td>
<td>Phase II; 53 patients with advanced non-GIST STS received 37.5 mg of sunitinib daily</td>
<td>1 patient with SD at 16 weeks</td>
<td>4</td>
<td>George et al (2009)</td>
</tr>
<tr>
<td>Cediranib</td>
<td>VEGFR-1–3, c-KIT</td>
<td>Phase I; 16 patients (age 8–18) with refractory solid tumors, including STS</td>
<td>1 PR with 67% tumor reduction</td>
<td>2</td>
<td>Fox et al (2010)</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>EGFR</td>
<td>Phase II/II; 46 patients with SS resistant to doxorubicin were assigned to 500 mg of gefitinib.</td>
<td>10 patients with SD; 6-month PFS, 6%</td>
<td>46, EGFR IHC +; no amplification/mutation</td>
<td>Ray-Coquard et al (2008)</td>
</tr>
<tr>
<td>Cixutumumab</td>
<td>IGF1R</td>
<td>Phase II; 113 patients with pretreated advanced and metastatic STS and Ewing family tumors received 10 mg/kg of cixutumumab every other week</td>
<td>3-month PFS, 18%; 1 patient with a PR, 6 patients with SD (2 lasting more than 12 weeks)</td>
<td>13, IGF1R NA</td>
<td>Schöffski et al (2013)</td>
</tr>
<tr>
<td>Ridaforolimus</td>
<td>mTOR</td>
<td>Phase III; randomly assigned to placebo, maintenance study of patients with advanced STS, responding to chemotherapy after four cycles; 40 mg of ridaforolimus daily (SUCCEED)</td>
<td>23 patients with SS in the ridaforolimus arm and 37 in placebo arm; PFS: 28% response rate reduction associated with ridaforolimus (HR 0.72; p= .001)</td>
<td>60</td>
<td>Demetri et al (2013)</td>
</tr>
<tr>
<td>Temsirolimus/cixutumumab</td>
<td>mTOR, IGF1R</td>
<td>Phase II; 388 patients with metastatic STS and bone sarcoma, first line; weekly treatment with cixutumumab (6 mg/kg intravenously) and temsirolimus (25 mg, intravenous flat dose) in 6-week cycles</td>
<td>ORR: 0%; 3 with tumor shrinkage</td>
<td>18, 78% IGF1R+</td>
<td>Schwartz et al (2013)</td>
</tr>
<tr>
<td>Tazemetostat</td>
<td>EZH2</td>
<td>Phase II; metastatic SS with evidence of SS18 rearrangement; 800 mg of tazemetostat orally twice daily</td>
<td>ORR: 0%; 11 patients with SD (33%; 5 patients with SD lasting 16 weeks or longer)</td>
<td>33</td>
<td>Schöffski et al (2017)</td>
</tr>
</tbody>
</table>

Abbreviations: SS, synovial sarcoma; PDGFR, platelet-derived growth factor receptor; VEGFR, VEGF receptor; SD, stable disease; PFS, progression-free survival; STS, soft tissue sarcoma; PR, partial response; NA, applicable; HR, hazard ratio; GIST, gastrointestinal stromal tumor; IHC, immunohistochemistry; ORR, overall response rate.

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such as the intraperitoneum, the retroperitoneum, or the paraspinal fat.1 MLPS can be accurately diagnosed because of a characteristic translocation t(12;16)(q13;p11) involving the DDIT3 and FUS genes, with smaller numbers harboring EWSR1-DDIT3 fusions. Beyond its radiosensitivity, the hallmark of MLPS is chemosensitivity to anthracyclines in combination with ifosfamide or dacarbazine and to single-agent trabectedin.6,34-37 In a small retrospective study that included 27 patients treated with doxorubicin and ifosfamide, partial response reached 43% and 86% per RECIST and Choi criteria, respectively.6 A similar response per RECIST was seen with dacarbazine in another small retrospective study.35 Of note, in MPLS, the high response rate to trabectedin (50%) also translated into a median progression-free survival (PFS) of 17 months; this suggests that trabectedin exerts a targeted, rather than a general, cytotoxic effect.34,36 It has been proposed that in MPLS trabectedin has the ability to displace the FUS-DDIT3 fusion protein from its target allowing for fat maturation on imaging and confirmed by increased peroxisome proliferator–activated receptor γ levels.36,38

Importantly, the activity of trabectedin and epirubicin in combination with ifosfamide in MLPS has been confirmed in the adjuvant/neoadjuvant setting as well, with similar disease-free survival after epirubicin combined with ifosfamide and trabectedin for a subgroup of 64 patients with MPLS treated within this histology-driven neoadjuvant randomized trial.37 Immunotherapy in MLPS is discussed in the section below.

Well-Differentiated Liposarcoma/Dedifferentiated Liposarcoma

Liposarcomas account for approximately 15% of STS. WDLPS/DDLPS represents about one-half of all liposarcomas. WDLPS/DDLPS harbors a supernumerary circular (“ring”) and giant elongated chromosomes that contain amplification of the 12q14-15 region, including the MDM2 gene and CDK4, often hundreds of copies are present.39

Doxorubicin-based treatment40 is first-line standard of care for nonoperable DDLPS high-grade liposarcoma, whereas trabectedin is used in second-line treatment.31 Eribulin also has regulatory approval for use in advanced liposarcoma and is perhaps most active in DDLPS.42

Other targeted compounds used to treat WDLPS/DDLPS include the CDK4/CDK6 inhibitor palbociclib, which was first given to patients with a proven CDK4 amplification and later amended as a result of its almost inherent presence in DDLPS.14 Among 60 treated patients with WDLPS/DDLPS whose disease progressed over the past 6 months, one complete response was reported, with PFS of 57% at 12 months and median PFS reaching 17.9 months. Therefore, from a practical perspective, CDK4/6 inhibitors like palbociclib should mainly be regarded as a disease stabilizer of limited use when dimensional response is desirable. In practice, they may serve as a strategy to delay surgery.

The first-in-class MDM2 inhibitor nutlin-3A prevents MDM2 association with p53 but its poor bioavailability and high toxicity limited its development. RG7112 is the most developed in this class of compounds.43 With a short 3-month neoadjuvant course, there was one partial response and there were 14 patients with stable disease with mainly hematologic grade 3 to 4 toxicity.13 RG7112 in combination with doxorubicin was evaluated in a phase I study of patients with STS and results are eagerly awaited (NCT01605526).

A novel way to impact p53 is through inhibiting the chromosome region maintenance 1 protein (CRM1). CRM1, a major export factor between the nucleus and cytoplasm, exports proteins with tumor suppressor activity such as p53.

### TABLE 2. Treatment Efficacy in Solitary Fibrous Tumors (RECIST)

<table>
<thead>
<tr>
<th>Treatment Type, Reference</th>
<th>Study Type</th>
<th>Patients, n</th>
<th>Partial Response</th>
<th>Stable Disease</th>
<th>Progressive Disease</th>
<th>Median PFS, Months</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazopanib57</td>
<td>Phase II</td>
<td>13</td>
<td>9</td>
<td>73</td>
<td>18</td>
<td>4.7</td>
<td>Median PFS, 13.3 months</td>
</tr>
<tr>
<td>Sunitinib11</td>
<td>Retrospective</td>
<td>31</td>
<td>6</td>
<td>51</td>
<td>42</td>
<td>6 (1–22)</td>
<td>Median PFS, 6 months</td>
</tr>
<tr>
<td>Sorafenib14</td>
<td>Phase II</td>
<td>5</td>
<td>0</td>
<td>40</td>
<td>60</td>
<td>Median treatment duration, 6.3</td>
<td>Median overall survival, 19.7 months</td>
</tr>
<tr>
<td>Dacarbazine60</td>
<td>Retrospective</td>
<td>8</td>
<td>37</td>
<td>50</td>
<td>12</td>
<td>7 (2–12)</td>
<td></td>
</tr>
<tr>
<td>Trabectedin61</td>
<td>Retrospective</td>
<td>11</td>
<td>9</td>
<td>73</td>
<td>18</td>
<td>11.6</td>
<td>Median overall survival, 22.3 months</td>
</tr>
<tr>
<td>Doxorubicin/dacarba-zine62</td>
<td>Retrospective</td>
<td>12</td>
<td>50</td>
<td>8</td>
<td>42</td>
<td>6.3 (2–32)</td>
<td>Median overall survival, 19 months</td>
</tr>
<tr>
<td>Temozolomide/bevacizumab12</td>
<td>Retrospective</td>
<td>14</td>
<td>79</td>
<td>14</td>
<td>7</td>
<td>9.7</td>
<td>Assessed by Choi</td>
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Abbreviation: PFS, progression-free survival.
Angiosarcoma

Angiosarcoma accounts for less than 2% of all STS and may present in a variety of ways. Angiosarcoma often arises as a primary cutaneous or soft tissue tumor (e.g., angiosarcomas of the liver and scalp). It may also develop as secondary to radiation therapy (e.g., radiation-associated angiosarcoma; commonly affecting the breast or chest wall after adjuvant irradiation for breast cancer or ductal carcinoma in situ) or secondary to chronic lymphedema (e.g., Stewart-Treves syndrome). The outcome of angiosarcoma is poor whether the tumor presents as metastatic or localized disease, with more than 40% of patients experiencing a disease relapse after surgery for primary resectable disease. Doxorubicin-based chemotherapy, weekly paclitaxel, and gemcitabine are regarded as the preferred therapeutic options for advanced angiosarcoma. Administration of weekly paclitaxel was assessed for 30 patients within a phase II trial: the median PFS and the median overall survival were 3.8 and 8.3 months, respectively, with a nonprogression rate of 24% at 6 months. A European Organization for Research and Treatment of Cancer review reported a response rate of 62% for 32 patients treated with weekly paclitaxel. In a retrospective series of 25 patients with advanced angiosarcoma, gemcitabine showed an impressive overall response rate of 68% with a median overall survival of 17 months.

Unsurprisingly, angiogenic signaling pathways play a role in angiosarcoma proliferation. Angiosarcoma overexpresses VEGFs, VEGF-A, and multiple VEGFRs, including the major proangiogenic VEGFR-1 and VEGFR-2. Some studies have reported recurrent activating mutations in angiogenesis signaling genes, especially VEGFRs. In addition to pazopanib, sorafenib was examined prospectively among pretreated patients with angiosarcoma and showed limited antitumor activity, with a 23% response rate and a median PFS of only 3.8 months in a subgroup of patients with visceral angiosarcoma. Finally, an open-label, randomized phase II trial explored the activity of bevacizumab administered concurrently with weekly paclitaxel and continued as maintenance until progression and compared it with single-agent weekly paclitaxel. No PFS benefit was seen with the addition of bevacizumab (6-month PFS rates of 54% in the paclitaxel-control arm and 57% in the bevacizumab arm) and median overall survival was 4 months shorter in the bevacizumab arm (19.5 months in the paclitaxel-control arm and 15.9 months in the bevacizumab arm).

The poor outcome of these patients and the limited activity of antiangiogenic drugs, particularly in vascular cancer, suggest multiple redundant survival pathways. One of these escape pathways is through endoglin, which allows continued angiogenesis despite VEGF inhibition. A recent report on a drug that targets endoglin, carotuximab (TRC105), demonstrated clinical improvement when combined with pazopanib in pretreated patients with angiosarcoma; durable and complete responses were particularly seen for patients with cutaneous angiosarcoma. A multicenter phase III trial of these agents is ongoing (NCT02979899).
HISTOLOGY-DRIVEN TREATMENTS: SUBTYPES WHERE CHEMOTHERAPY AND ANTIANGIOGENIC AGENTS ARE ACTIVE

Solitary Fibrous Tumors

SFTs, sometimes still termed hemangiopericytoma in some anatomic sites, are fibroblastic tumors originating in adults age 20 and older. Although most SFTs treated surgically do not recur, at least 10% to 20% have more aggressive features, including hypercellularity, infiltrative margins, necrosis, and four or more mitoses per high-power field. An NAB2-STAT6 gene fusion was established as the defining genetic alteration and the diagnostic marker of SFTs. In normal cells, NAB2 and STAT6 are adjacent genes on chromosome 12q13. In the context of SFTs, the NAB2 fusion protein acquires an activation domain from the signaling molecule STAT6, converting a transcriptional repressor (NAB2) into a potent transcriptional activator of the early growth response family of genes. Early growth response target genes including FGFR1 and NTRK1 are overexpressed in SFTs (Doege-Poerner syndrome). Positive nuclear STAT6 immunoreactivity is highly sensitive and specific for the diagnosis of SFTs because of its exceeding abundance in the nucleus of these cells. This suggests that Janus kinase inhibitors inhibiting STAT6 phosphorylation could be an attractive targeted therapeutic option. However, STAT6 accumulates in the nonphosphorylated form in the nucleus of SFT cells, rendering Janus kinase inhibition activity redundant.

Activity with antiangiogenic agents or chemotherapy has been demonstrated in SFTs. Although the mechanism of action of antiangiogenic agents in SFTs is still to be defined, antiangiogenic agents such as pazopanib, sunitinib, and sorafenib are shown to be active in this entity, with PFS of approximately 6 months (Table 2). In addition, although doxorubicin alone has been disappointing in this entity, better results were reported with dacarbazine, trabectedin, and dacarbazine in combination with doxorubicin. A prospective trial comparing dacarbazine/doxorubicin with trabectedin is ongoing (NCT03023124). Currently, the highest clinical benefit rate based on Choi criteria (93%) was seen in a retrospective series from The University of Texas MD Anderson Cancer Center, in which an antiangiogenic agent, bevacizumab, was combined with temozolomide.

HISTOLOGY-DRIVEN TREATMENTS: SUBTYPES RESISTANT TO CHEMOTHERAPY AND SENSITIVE TO TARGETED THERAPY AND/OR ANTIANGIOGENIC AGENTS

Perivascular Epithelioid Cell Neoplasms

PEComas are a group of related tumors, the members of which include angiomyolipoma of the kidney, clear cell sugar tumor of the lung, and lymphangioleiomyomatosis. This family of tumors is composed of perivascular epithelioid cells, with coexpression of melanocytic markers (e.g., HMB45, Melan-A, and tyrosinase) and muscle markers (e.g., myomelanocytic immunophenotype). PEComas include neoplasms harboring TFE3 gene rearrangements and those with TSC1 and TSC2 mutations, indicating alternative tumorigenic pathways.

Mutations in TSC1 and TSC2 disrupting the mTOR signaling pathway led to exploration of mTOR inhibitors in PEComas. Small case series with sirolimus or temsirolimus were reported. Wagner et al reported significant clinical responses among three patients treated with sirolimus, and Batera et al describe prolonged radiological complete remission (52 months) in a patient with advanced PEComa following treatment with sirolimus. Ten patients were included in the retrospective study from the Royal Marsden Hospital. Among the seven evaluable patients for response, 70% achieved partial response (one with temsirolimus and six with sirolimus). Of note, two out of the three nonevaluable patients in the study progressed within the first 16 days of sirolimus, too quickly for evaluation. Results of a prospective phase II trial of ABI-009 (nab-rapamycin) for patients with advanced malignant PEComas are awaited (NCT02494570). PEComas are considered less responsive to chemotherapy, with one abstract reporting a short-lived (PFS of 2.8 months) 25% partial response following gemcitabine-based chemotherapy.

Alveolar Soft-Part Sarcoma

ASPS is a rare, slowly growing sarcoma that has a propensity to metastasize to the brain in addition to the lungs. A characteristic unbalanced translocation t(X;17)(p11;q25), which fuses ASPSCR1 to TFE3, leads to an increase in MET transcription that, upon extracellular hepatocyte growth factor binding, activates pro-oncogenic intracellular signaling pathways such as mTOR/AKT and RAS/RAF/MEK1/2.

Despite the indolent nature of the ASPS, eventually progression occurs and therapy is required. Chemotherapy has been disappointing and is not currently a standard part of management in the clinic. A recent retrospective report by Stacchiotti et al demonstrated limited benefit with trabectedin: 4% achieved partial response, 56% had disease stabilization, and 39% progressed. Median PFS was 3.7 months, with only 13% remaining progression-free at 1 year.

Consistent benefit from different tyrosine kinase inhibitors (sunitinib, cediranib, and anlotinib and pazopanib) was reported in several studies. For example, in a retrospective study evaluating pazopanib, among the 29 evaluable patients (13 of whom were previously treated with an antiangiogenic), 3% had a complete response, 24% had a partial response, and 58% had disease stabilization. Median PFS was 13.6 months (range, 1.6–32.2+) and 59% remained progression-free at 1 year.

The inherent overexpression of MET in ASPS led to a study assessing tivantinib, a selective MET inhibitor, for patients with ASPS. The reported disease control rate was 78% with a median duration of response of 6 months (range, 2–30; Fig. 1).

Current clinical trials are recruiting patients to studies that compare two different tyrosine kinase inhibitors, cediranib...
and sunitinib (NCT01391962), or combine a tyrosine kinase inhibitor with an anti–PD-1 agent, axitinib and pembrolizumab (NCT02636725), and evaluate a single anti–PD-L1 agent, atezolizumab (NCT03141684). The results of these trials are awaited.

Inflammatory Myofibroblastic Tumors
IMTs are a heterogenous group of tumors with a propensity to develop in soft tissue and viscera. Because the morphologic hallmark of IMT is the coexistence of myofibroblastic spindle cells and an infiltrate of immune cells, it is of interest that human herpesvirus-8 DNA sequences accompanied by overexpression of human interleukin (IL)-6 and cyclin-D1 were reported in these tumors.

The unique genetic background of IMTs includes ALK, c-ros oncogene 1, receptor tyrosine kinase (ROS), and kinesin family member 5B (KIF5B)-ret proto-oncogene (RET) gene rearrangements in approximately 50% of cases. Interestingly, these fusions are more prevalent among children and young adults, whereas 90% of older patients have fusion-negative IMTs associated with a more aggressive course and a higher frequency of metastases. IMTs with ALK genomic rearrangements show constitutive activation and overexpression of the ALK kinase domain, which induces tumorigenesis cell proliferation and survival through downstream activation of intracellular signaling pathways.

Crizotinib activity was initially documented in a case report of an adult patient with an IMT harboring an ALK translocation and confirmed in a phase I/II trial of pediatric patients, with complete and partial response rates of 36% and 50%, respectively, for a median duration of treatment of more than 1.5 years. More recently, ceritinib was reported to extend the disease-free interval for a patient with acquired resistance to crizotinib.

Clear Cell Sarcoma
Clear cell sarcoma (CCS) belongs to the family of microphthalmia transcription factor–associated tumors. These tumors are characterized by the activation of microphthalmia transcription factor, which activates transcription of c-Met, an oncogenic tyrosine kinase receptor. In CCS, increased c-MET expression (and in some instances, increased expression of its ligand hepatocyte growth factor) results from the typical chimeric protein of t(12;22)(q13;q12) (EWSR1-ATF1) translocation, which increases transcription of the microphthalmia transcription factor. CCS oncogenesis is dependent on hepatocyte growth factor/c-Met signaling. Previous studies showed that inhibition of Met signaling reduced CCS cell growth in vitro and in vivo. The fact that CCS is notorious for being chemotherapy and radiotherapy resistant and the finding that CCS survival is dependent on Met signaling were the rationale for exploring Met tyrosine kinase receptor inhibitors. Tivatinib (ARQ197)
was studied in a phase II trial with 11 patients with CCS. The disease control rate reached 36% (one patient achieved a partial response), whereas the median response lasted 3 months. Activity of crizotinib, another small molecule that has Met receptor inhibitory activity among its targets, was recently assessed in a phase II basket trial (EORTC 90101) that included a cohort of 26 patients with CCS. Although the primary endpoint of the study (response rate) was not met (3.8%; 1 of 26 had a partial response), disease control was achieved for 69% of patients (18 of 26) with fluorescent in situ hybridization–confirmed EWSR1 rearrangement for a median of 131 days.7

Although disease stabilization is the main outcome in this case, further studies combining inhibitors of signaling pathways downstream to the Met receptor (e.g., mTOR or MEK) may improve and extend activity.

**HISTOLOGY-DRIVEN TREATMENTS: IMMUNOTHERAPY**

**The Diversity of the Sarcoma Immune Microenvironment**

Sarcoma subtypes differ markedly with respect to inflammatory gene expression, immune cell infiltration, and their T-cell repertoires.81 This diversity in the sarcoma tumor microenvironment necessitates the development of a subtype-specific targeted approach for immunotherapy. Undifferentiated pleomorphic sarcoma (UPS) has a relatively high mutation burden. Like other highly mutated cancers with an inflammatory tumor microenvironment,82 these tumors have high levels of PD-1 and PD-L1 expression and a high T-cell fraction based on T-cell receptor (TCR) sequencing of the TCR Vβ region. TCR sequencing data have also demonstrated a high clonality in UPS tumors, suggesting a “focused” T-cell response with expansion of high-affinity clones targeting immunogenic mutated proteins. This T-cell–driven inflammatory response contrasts markedly with the translocation-associated sarcoma subtypes synovial sarcoma and MLPS, which have a far less inflammatory microenvironment with much less T-cell infiltration or PD-1 or PD-L1 expression and markedly lower levels of genes related to antigen presentation.81

**Immunotherapy for Undifferentiated Pleomorphic Sarcoma and Dedifferentiated Liposarcoma: Responses to Checkpoint Inhibitors**

Although experience using checkpoint inhibitors in sarcoma is small relative to other cancers, this work is expanding rapidly. The SARC28 trial of single-agent pembrolizumab provides the largest published data set currently available regarding subtype-specific responses to PD-1–targeted therapy.83 The trial treated four separate STS cohorts with 10 patients each, including UPS, leiomyosarcoma, DDLPS, and synovial sarcoma. The trial saw partial responses in four of 10 patients with UPS and two partial responses in patients with DDLPS. A very temporary response was also seen in a patient with synovial sarcoma. Responses seem to be PD-L1 independent, because PD-L1 was positive in only two of six responders. The combination of anti–CTLA-4 and PD-1 blockade can create dramatic synergy, albeit with considerably increased toxicity in some tumor types.84,85 Preliminary results of the Alliance trial combining nivolumab and ipilimumab (at a 1-mg/kg dose of ipilimumab) appeared to also show promising results with considerably less toxicity than similar studies using higher doses of ipilimumab.86 An ongoing trial at MD Anderson Cancer Center is testing a similar approach using durvalumab and tremelimumab (NCT02815995).

Combinations with chemotherapy are being tested and may further potentiate this response. Sarcomas tend to lack infiltrating regulatory T cells; however, this may be different following checkpoint blockade. Because low-dose cyclophosphamide can kill regulatory T cells and can be an effective agent in sarcoma treatment, metronomic cyclophosphamide was tested in combination with pembolizumab.87 The trial did not meet its endpoints with respect to response rate.

Other combination studies of chemotherapy with checkpoint blockade are currently ongoing. Doxorubicin can result in immunogenic tumor cell death with the release of damage-associated molecular patterns that can be highly inflammatory. Furthermore, although doxorubicin is highly myelosuppressive, its lymphodepleting effect is less profound, which may be ideal in combination with a T-cell–targeted checkpoint blockade. Doxorubicin is currently being tested for sarcoma in combination with pembrolizumab (NCT03888665). Gemcitabine may eliminate monocytederived suppressor cells and may also similarly lead to immunogenic cell death (NCT03123276). An ongoing multiarm study is testing pembrolizumab with different chemotherapies: gemcitabine, gemcitabine and docetaxel, gemcitabine and vinorelbine, and liposomal doxorubicin (PembroPlus, NCT02331251).

Single-agent pembrolizumab will soon be tested in the neoadjuvant setting along with standard radiation in the multicenter, randomized SARC032 study for patients with UPS and DDLPS and a similar open-label, single-arm study is treating all STS subtypes at the Fred Hutchinson Cancer Research Center (NCT03338959).

A combination checkpoint inhibition in the neoadjuvant setting with durvalumab and tremelimumab plus radiation is being tested in a pilot trial with the University of Maryland (NEXIS, NCT03116529).

**Alveolar Soft-Part Sarcoma and Mismatch Repair**

Studies in colon cancer first demonstrated that microsatellite instability leads to a highly mutated, inflammatory microenvironment richly infiltrated with cancer-specific T cells.88 A study of 12 tumor types demonstrated that, regardless of a tumor’s site of origin, patients with mismatch repair deficiency had a much higher response rate to PD-1 blockade compared with other tumors, leading the U.S. Food and Drug Administration to approve pembrolizumab for tumors driven by microsatellite instability.89 Although the rate of microsatellite instability in sarcomas is extremely...
Leiomyosarcoma and Other STS Tumors With Macrophage-Driven Immune Evasion
Based on the characteristics of the tumor microenvironment, leiomyosarcoma should be an ideal target for immunotherapy. These tumors have T-cell infiltration and frequently express high levels of PD-L1 on tumor cells, with high levels of PD-1–expressing T cells. However, SARC28 study investigators did not see responses in leiomyosarcoma, and a study of nivolumab for the treatment of advanced leiomyosarcoma had only a single responding patient who ultimately developed a PTEN mutation that led to treatment resistance. Some investigators have suggested that the general failure of leiomyosarcoma tumors to respond to PD-1 blockade may be a result of heavy tumor infiltration by tumor-associated macrophages (TAMs). Interestingly, PD-1 and PD-L1 expression has also been correlated with macrophage infiltration. TAMs may be completely or incompletely polarized to classic macrophages (M1), which can directly kill tumors and aid infiltrating T cells, or alternative macrophages (M2), activated TAMs that inhibit the T-cell response through secretion of IL-10 and transforming growth factor β. Although TAMs likely play a major part in immune resistance for many sarcoma types, the M2-type TAM-associated gene signatures are found frequently in leiomyosarcoma tumors and high levels have been correlated with worse clinical outcomes among patients with leiomyosarcoma.

Because TAMs appear to play a key role in supporting the STS microenvironment, there has been interest in applying therapies that can either deplete M2 TAMs or transfer TAMs from a M2 to M1 phenotype. To this end, a Toll-like receptor 4 agonist, glycoursoyl lipid A, was directly injected into STS tumors, a majority of which were leiomyosarcoma. As presented at the 2016 ASCO Annual Meeting, many patients who received the intratumor injection of this agonist were found to have conversion of M2-type macrophages to M1-type macrophages, resulting in a high degree of local tumor control. CD47 is an antigen expressed by tumor cells that binds to signal-regulatory protein alpha on macrophages and inhibits macrophage-mediated tumor cell phagocytosis. Trials targeting anti-CD47 with a monoclonal antibody (Hu5F9-G4), such as NCT02216409, are open for all solid tumors and may be well suited for patients with leiomyosarcoma.

M2 TAMs frequently express the CSF1R kinase, c-Fms (CD115), which has been targeted using PLX3397 in models of malignant peripheral nerve sheath tumors, where TAMs also appear to play a key role. This compound is being examined in a phase I study of the combination of PLX3397 and sirolimus for patients with STS (NCT02584647).

Based on the antitumor activity that has been seen with the U.S. Food and Drug Administration–approved drug, trabectedin, a trial combining trabectedin and anti–PD-L1 inhibition for patients with liposarcoma and leiomyosarcoma is currently underway (NCT03074318). The combination of trabectedin with both ipilimumab and nivolumab is being tested at the Sarcoma Oncology Center in Santa Monica, California (NCT03138161).

Targeting NY-ESO-1: Synovial Sarcoma and Myxoid/Round Cell Liposarcoma
SS and MLPS are both immunologically quiet tumor types with low expression levels of inflammatory genes, low levels of major histocompatibility complex, and few infiltrating T cells. However, these tumors are thought to be excellent candidates for antigen-specific immunotherapy because they typically express high levels of the immunogenic cancer-testis antigens NY-ESO-1. Cancer-testis antigens are heterogeneously expressed in approximately 20% to 30% of many tumor types, including ovarian cancer, lung cancer, and melanoma. However, synovial sarcoma and MLPS may be particularly well suited to these types of approaches because antigen is homogenously expressed in more than 80% of synovial sarcoma and MLPS tumors. NY-ESO-1 is being targeted through a number of strategies including vaccine-based approaches and adoptive T-cell–type strategies.

Multiple groups have tried to use vaccination to induce NY-ESO-1–specific T cells in malignancies such as ovarian cancer and melanoma. However, expression of antigen in the cytoplasm of the antigen-presenting cell can lead to a far more potent CD8 T-cell response. LV305, a novel hybrid viral vector that encodes NY-ESO-1, is designed to target dendritic cells in vivo and stimulate CD8 T cells against NY-ESO-1. The vector genomic backbone is a lentiviral vector modified to be replication incompetent and integration deficient. The vector selectively targets DC-SIGN (CD209) on human dendritic cells via its envelope, a glycoprotein derived from Sindbis virus. The first patient treated with LV305 had a dramatic and durable response. The early encouraging results with this vector led to the first combined vector along with a potent Toll-like receptor 4 agonist and an NY-ESO-1 protein vaccine in a “prime-boost” regimen known as CMB305. This regimen was then further combined with atezolizumab, an anti–PD-L1 inhibitor, in a randomized phase II study (Fig. 2). An interim analysis indicated that the addition of CMB305 to atezolizumab resulted in improved clinical efficacy over atezolizumab alone for patients with NY-ESO-1+ STS with low PD-L1. There were three of 45 partial responses in synovial sarcoma for patients treated with the combination versus none in the group treated with...
atezolizumab alone.\textsuperscript{116} A phase III trial is planned to test the CMB305 regimen in the maintenance setting after frontline chemotherapy in the metastatic setting for patients with synovial sarcoma. Another promising NY-ESO-1 vaccine linked to a monoclonal antibody directed to CD205, which is expressed on dendritic cells, has also been tested in solid tumors including a small group of patients with sarcoma with some early signs of immunogenicity.\textsuperscript{117}

Adaptive cellular transfer of tumor-specific T cells has the potential to eliminate solid tumor malignancies.\textsuperscript{118,119} In a pilot study testing a high-affinity, NY-ESO-1–specific Toll-like receptor, patients with pretreated advanced melanoma and synovial sarcoma received engineered T cells following lymphodepletion with cyclophosphamide and fludarabine as well as post-treatment high-dose IL-2.\textsuperscript{120} Objective clinical responses were seen for 45% (5 of 11) and 67% (4 of 6) of patients, respectively, without any incidences of toxicity attributable to the cells. This study included six patients with synovial sarcoma as well as some with melanoma. Updated results were reported in 2015, with respective overall response rates for 55% (11 of 20) and 61% (11 of 18) of patients with melanoma and synovial sarcoma, respectively.\textsuperscript{107} Adaptimmune Therapeutics continues to study this Toll-like receptor and trials are ongoing (NCT01343043).

Finally, engineered Toll-like receptor have emerged as a powerful and potentially curative therapy for patients with HLA-A*02+ with synovial sarcoma\textsuperscript{121} and MLPS\textsuperscript{122} expressing NY-ESO1. Two studies were presented at the ASCO and Connective Tissue Oncology Society annual meetings.\textsuperscript{123,124} The overall response rate was high in both subtypes, but this approach has the limitation of being human leukocyte antigen restricted. The ongoing Adaptimmune study is using peptide-enhanced affinity (SPEAR) NY-ESO1 T cells that are centrally made and shipped to multiple sites.

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Multidisciplinary Management of Oligometastatic Soft Tissue Sarcoma

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OVERVIEW

Soft tissue sarcomas (STS) encompass a group of rare but heterogeneous diseases. Nevertheless, many patients, particularly those with oligometastatic disease can benefit from thoughtful multimodality evaluation and treatment regardless of the STS subtype. Here, we review surgical, interventional radiology, radiation, and chemotherapy approaches to maximize disease palliation and improve survival, including occasionally long-term disease-free survival. Surgical resection can include lung or other visceral, soft tissue and bone metastases with a goal of rendering the patient disease free. Staged resections can be appropriate, and serial resection of oligometastatic recurrent disease can be appropriate. Retrospective series suggest survival benefit from this approach, although selection bias may contribute. Interventional radiology techniques such as percutaneous thermal ablation (PTA) and arterial embolization can present nonoperative local approaches in patients who are not medically fit for surgery, surgery is too morbid, or patients who decline surgery. Similarly, radiation therapy can be delivered safely to areas that are inaccessible surgically or would result in excessive morbidity. Currently no randomized trials exist comparing interventional radiologic approaches or radiation therapy to surgery but retrospective reviews show relatively similar magnitude of benefit in terms of disease palliation and survival, although it is felt unlikely that these procedures will render a patient to long-term disease-free status. Chemotherapy has evolved recently with the addition of several new treatment options, briefly reviewed here. Importantly, if a patient sustains a good response to chemotherapy resulting in true oligometastatic disease, consideration of multimodality local therapy approaches can be considered in the appropriate patient.

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal malignancies diagnosed in approximately 13,000 patients and resulting in 5,000 deaths in the United States annually. With over 50 histologic subtypes, each harboring unique molecular drivers and biologic behavior, the National Comprehensive Cancer Network guidelines recommend a multidisciplinary team experienced in caring for these rare cancers. Approximately 90% of patients with STS present with localized disease, although many will develop metastatic disease, which is typically the cause of death. Most STS show a predilection for metastasizing to the lungs, but certain histologies spread to the lymph nodes (rhabdomyosarcoma and synovial sarcoma), bone (myxoid liposarcoma), and abdomen (myxoid round cell liposarcoma).

When patients develop recurrent metastatic disease after successful treatment of the primary sarcoma, factors impacting prognosis and the modality of therapy include location, number, and time to development of metastasis. It is critical to rule out other benign or malignant etiologies (e.g., primary lung cancer), particularly when there is a longer disease-free survival (DFS) interval. Tissue diagnosis may occur at the time of a therapeutic procedure, such as surgical resection or RFA, or from an image-guided core needle biopsy. Multiple new lung masses within 6 months of therapy for a primary sarcoma indicate that the tumor has metastasized, and systemic therapy should be considered. Because treatment of sarcoma metastasis can be tailored to specific sarcoma histology, pattern, and number of metastases and the DFS interval preceding developing metastasis, such patients should be managed by an experienced multidisciplinary team to best assess how surgery, interventional radiology, radiation, and chemotherapy can be integrated into the treatment to improve survival, palliate symptoms, and occasionally render oligometastatic sarcoma a chronic disease.
SURGERY IN METASTATIC SARCOMA

Although the role of surgery applies most commonly to lung metastases, similar principles can be extrapolated to limited visceral, soft tissue, and bone metastases. Complete pulmonary metastasectomy is feasible in about 30% of patients with oligometastatic STS corresponding with long-term survival advantage.

Patient Selection

The general principles for pulmonary metastasectomy include the following:

- Complete resection of metastases is possible
- Limited extrathoracic disease that is also completely resectable
- Absence of multivisceral metastatic disease
- Primary tumor controlled/controllable
- Medical fitness for lung resection
- Medically fit surgical candidate

This information is obtained in the preoperative evaluation, which typically includes CT and/or PET/CT scan. Nodal and extrathoracic disease should be aggressively diagnosed and managed. Occult lymph node involvement is rare, and systematic lymph node assessment is not generally performed.

Techniques

For a patient determined to be a good candidate for metastasectomy, the choice of surgical technique is dictated by surgeon preference and experience. Regarding pulmonary metastases, a thoracotomy allows the surgeon to palpate the entire lung for additional nodules. However, with current high-definition imaging techniques, the overall likelihood of identifying radiographically occult disease intraoperatively is low, and surgeons experienced with video-assisted thoracoscopy can also use instruments to palpate the lung.

Additionally, initially unrected metastases may be subsequently resected when they become detectable on CT scan without reducing survival. Subsequent thoracic operations are less difficult following prior video-assisted thoracoscopy than following a thoracotomy. Choice of wedge resection, segmentectomy, lobectomy, or rarely a pneumonectomy is dictated by that necessary to achieve complete metastatic clearance and the patient’s medical suitability for resection. Especially for extrapulmonary disease, given the advances in PTA and stereotactic body radiation therapy (SBRT) techniques, the value of metastasectomy should be weighed against the potential morbidity with regard to infection, local vital structures, and recovery.

Outcomes

Evidence of the effectiveness of pulmonary metastasectomy is based on registry data and retrospective studies, which often include epithelial carcinomas such as colorectal cancer. The International Registry of Lung Metastases found similar survival rates after pulmonary metastasectomy in patients with epithelial carcinomas and in those with sarcomas.

The European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group conducted a retrospective multi-institutional study of 255 patients with STS who underwent pulmonary metastasectomy. Three- and 5-year overall survival (OS) rates were 54% and 38%, respectively, whereas corresponding DFS rates were 42% and 35%, respectively.

Prognostic factors associated with improved survival after pulmonary metastasectomy are fairly consistent across studies. These include the following:

- Ability to achieve complete resection
- Limited number of nodules (< 3)
- Long interval (> 12 to 18 months) between primary tumor resection and development of metastatic recurrence
- Small tumor size (< 2 cm)
- Low-grade histology

PRACTICAL APPLICATIONS

- Oligometastatic STS is best approached as a multimodality disease, benefiting from evaluation and possible treatment with surgery, interventional radiology, radiation therapy, and chemotherapy.
- If the patient is expected to be able to be rendered disease free, surgical resection of oligometastatic STS remains an appropriate standard option for the medically fit and resectable patient.
- Interventional radiology techniques including radiofrequency ablation (RFA) and arterial embolization provide nonoperative local modality alternatives that can provide good disease control.
- The role of radiation with local therapy of primary STS is well established and discussed elsewhere. Radiation can also provide a nonoperative local modality alternative for oligometastatic disease that can achieve durable and noninvasive disease control.
- Chemotherapy remains an appropriate choice in this setting as well.

One single-institutional series of 214 patients who underwent pulmonary metastasectomy identified three unfavorable risk factors: tumor size more than 2 cm, more than one metastasis, and metastasis-free interval of less than 18 months. Patients with none of these risk factors had a 5-year survival of 60%, whereas those with one, two, or three of these had 30%, 20%, and 0% 5-year survival, respectively.

Most patients undergoing pulmonary metastasectomy for STS will ultimately develop recurrence, although this does not negate the value of resection. In another single-institution series, 539 patients underwent 760 pulmonary metastasectomies for metastatic STS. The OS was 33 months, and 5-year survival was 34%. After R0 resection, 74% developed disease recurrence at any site, 63% developed lung recurrence, and 34% developed isolated lung recurrence.

Patients who develop recurrence following initial curative metastasectomy should be considered for repeat resection. In a series of 43 patients who underwent second thoracotomy for pulmonary metastasectomy, the OS was 25 months...
for the 72% undergoing curative complete resection versus 10 months for those not completely resectable. A study from the International Registry of Lung Metastases (including epithelial carcinomas) found that 53% of the 5,206 patients undergoing resection of pulmonary metastases relapsed in the lung. Among the 1,042 patients who underwent repeat metastasectomy, the 5- and 10-year OS were 44% and 29%, respectively. Demonstrating the negative impact of disease burden, the median survival among patients who were not resected following relapse in one series was 8 months. In a second series, in 39 patients who underwent repeat metastasectomy, OS for the 19 patients with single-site disease was 65 months, compared with 14 months for the 15 patients with two or more sites of recurrence. Although clearly demonstrating benefit, these retrospective series are subject to patient selection bias favoring patients who are fit and eligible for metastasectomy.

**INTERVENTIONAL RADIOLOGY IN METASTATIC SARCOMA**

The role of the interventional radiologist in the treatment of metastatic sarcoma is expanding. Image-guided therapies for metastatic sarcoma, such as PTA and arterial embolization, may be alternatives or adjuncts to surgery or radiation therapy in patients with solitary or oligometastatic disease.

**Patient Selection**

Potential candidates should be reviewed with an interventional radiologist to determine feasibility and appropriateness of therapy. PTA is currently reserved for patients who are not surgical candidates, have electively refused surgery, or have failed other treatment options. PTA is minimally invasive and can be performed in an outpatient setting with fewer complications, decreased morbidity, and reduced recovery time compared with surgery. With ablation, there is no treatment-specific toxicity. PTA may be performed for new or growing lesions and can be repeated in the setting of local failure, an option often not available for surgical or radiation therapies.

The precise size and number of lesions appropriate for image-guided interventional therapies for metastatic sarcoma have yet to be defined. Optimal lesion characteristics for successful treatment have been derived from nonsarcoma primaries and vary based upon the site of metastasis. For example, in the lung, best results are achieved in patients with four or fewer metastases and target lesion size less than 3 cm, whereas similar local control rates may be obtained in the liver with larger lesions. Lesion proximity to critical structures, such as the heart, diaphragm, or bowel, is an important consideration for safety and may preclude ablative options.

**Techniques**

**Ablative therapies.** Several techniques for PTA are available and can be categorized as either burning (radiofrequency, microwave, laser, and high-intensity focused ultrasound) or freezing (cryoablation). With burning modalities, temperatures greater than 50°C produce denaturing of cellular proteins and damage to cell membranes, resulting in coagulation necrosis and tumor cell death. Cryoablation incites cytotoxicity by freezing rather than heating tissues, with cell death occurring at −40°C secondary to ice formation within the extracellular matrix and lysis during thawing.

Published studies involving PTA are highly variable in design, with differing patient selection criteria, primary tumor, treatment algorithms, and follow-up intervals. Furthermore, direct comparison of outcomes to other local treatment strategies are difficult, as patients who had PTA typically have a higher risk profile than candidates for surgery or radiation, hence a strong selection bias affects outcomes interpretation. Notwithstanding, even within these limitations, the available data for PTA therapies are encouraging.

Radiofrequency ablation (RFA; Fig. 1) is the most widely reported ablative technique for treatment of metastatic sarcoma, with the majority of data pertaining to lung metastases. Reported local recurrence rates for RFA, microwave ablation, and cryoablation are variable at 0% to 15%, 2%, and 24%, respectively. Long-term efficacy of RFA for sarcoma metastases documented a 1- and 3-year survival of 92.2% and 65.2%, with a median DFS of 7 months. A European multicenter retrospective study found a substantial treatment benefit of PTA in patients with sarcoma oligometastatic disease; median survival for those treated with ablation was 45.3 months compared with only 12.6 months for those who did not have PTA. At least one series found the OS for RFA to be similar to surgical treatment of sarcoma metastases to the lung.

PTA has also emerged as an effective treatment of liver malignancies. Although published efficacy data for sarcomas are limited, hepatic ablation has a low-risk profile with good results, though local control is less than that of surgical resection. A small series evaluating PTA for hepatic gastrointestinal stromal tumor (GIST) metastases demonstrated up to 100% local control and 2-year progression-free survival (PFS) of 75% when combined with tyrosine kinase inhibitor therapy. Similar findings have been reported with RFA and cryoablation for liver metastases from other sarcoma histologies including leiomyosarcoma, fibrosarcoma, and synovial sarcoma.

High-intensity focused ultrasound is another form of thermal ablation that uses sound wave to generate heat through friction to achieve tumor necrosis. For sarcomas, high-intensity focused ultrasound has been evaluated for the treatment of both primary lesions and bone metastases. One of the largest series showed excellent local tumor control of 86.3% with overall 1-, 3-, and 5-year survival of 93%, 75%, and 64%, respectively.

**Embolization.** Arteries feeding metastases may be selectively embolized with microparticles, resulting in ischemia and tumor death. Image-guided arterial embolization therapies are primarily indicated for patients with unresectable sarcoma and isolated hepatic metastases or minimal extrahepatic disease. Techniques consist of bland embolization (occlusion of the vascular supply), chemoembolization...
(deposition of chemotherapeutic agents within the tumor), and radioembolization (deposition of a radiation source within the tumor).

Transcatheter arterial chemoembolization restricts the vascular supply to hepatic metastases by deploying embolic particles treated with chemotherapeutic agents. Minimal efficacy data are available; however, a small series of hepatic sarcoma metastasis treated with transcatheter arterial chemoembolization demonstrated excellent local control with 2- and 3-year survival rates of 54% and 50%, respectively.34

Radioembolization is a similar technique that deploys embolization particles coupled with a radiation source, commonly 90Y, to deliver sustained radiotherapeutic doses; it is most often performed in conjunction with hepatic resection or other therapies, including PTA. Although experience with sarcomas is limited, early results are promising, with partial or complete response found in 73% and 82% at 3 and 6 months, respectively.35

RADIATION THERAPY IN METASTATIC SARCOMA

Although sarcomas are sometimes mistakenly termed “radioresistant,” radiation therapy is a standard component of localized extremity STS treatment.36-38 When patients with sarcomas develop symptomatic metastases, radiation can palliate painful bony metastasis, hemoptysis from lung metastases, and neurologic symptoms that result from spinal cord compression. For patients with oligometastatic disease, image-guided radiation therapy is an alternative to surgery or PTA to eliminate sarcoma metastases.

The same technology used to deliver SBRT for safe and effective treatment of early-stage lung cancer39 can be applied to treat pulmonary metastases from sarcomas (Fig. 2). A retrospective review of 30 consecutive patients with sarcoma with 39 pulmonary metastases treated with SBRT with a median dose of 50 Gy given in four to five fractions found SBRT to be safe and effective.40 At 12 and 24 months, local control was 94% and 86%, respectively. In this heavily pretreated patient cohort (77% received prior chemotherapy, 70% had one to three prior pulmonary resections, and 26% had received prior thoracic radiotherapy), OS at 12 and 24 months was 76% and 43%, respectively. Three patients developed grade 2 chest wall toxicity, but there were no other grade 2 or greater toxicities. Similar results were obtained from an independent cohort of 28 patients with sarcoma with 51 lung metastases treated with SBRT.41 The actuarial 5-year rate of local control and 2-year OS were both 96%. No grade 3 or higher toxicities were observed. Taken together, these studies indicate that SBRT can be used to effectively treat oligometastatic sarcoma in the lungs. SBRT has also been applied to treat oligometastatic sarcoma metastases to the spine. A total of 88 consecutive patients with sarcoma were treated with SBRT for 120 spinal lesions.42 The 12-month actuarial rate of local DFS was 85.9%.

One advantage of using SBRT to treat oligometastatic metastases from sarcoma over surgery and PTA is that SBRT is noninvasive, although typically it requires a core needle biopsy to confirm diagnosis. In contrast, with surgical resection or PTA, the therapeutic procedure can be diagnostic. Nevertheless, because SBRT is noninvasive, compared with surgical resection, it causes less patient discomfort and
also has a lower 30- and 90-day postprocedure mortality. SBRT can also be delivered to anatomic sites that may not be amenable to surgery or PTA. Normal tissue radiation tolerance of the lungs and other organs must be respected, thus limiting the role of SBRT to treat a large number of lung metastases. If delivering SBRT would exceed normal tissue radiation tolerance because of the extent of metastatic disease, then systemic therapy should be considered.

CHEMOTHERAPY IN METASTATIC SARCOMA

Although most local therapy principles of oligometastatic disease apply across histologic subtypes, eventually many patients ultimately will progress such that they or their disease are not amenable or appropriate to local therapy. STS are rare and are composed of a heterogenous group of diseases and in part because of the relative paucity of molecular targets, effective systemic therapies remain a challenge. Despite this, recent progress has been made in identifying systemic agents in the treatment of STS. The goals of systemic therapy are often palliative in intent with a focus on improvements in symptoms related to the disease, PFS, and OS. Except for patient-specific need for tumor shrinkage for symptom improvement, overall response rate (ORR) predicts poorly for the therapeutic efficacy in STS. Importantly, most low-grade STS are chemotherapy resistant and generally excluded from chemotherapy trials.

HISTOLOGY-AGNOSTIC CHEMOTHERAPY

Doxorubicin-Based Approaches

For over 40 years, doxorubicin has been the backbone of many sarcoma regimens. Doxorubicin combinations including dacarbazine and ifosfamide show improvement in ORR but lack PFS and OS benefit. Recently, the fully humanized monoclonal antibody platelet-derived growth factor receptor α inhibitor olaratumab received accelerated U.S. Food and Drug Administration (FDA) approval based on an open-label phase IB/randomized II trial of 133 patients with advanced STS who received doxorubicin with or without olaratumab. This study achieved its primary endpoint of PFS 6.6 versus 4.1 months and an impressive improvement in OS of 25 versus 10.7 months for the combination versus monotherapy, respectively. Of note, patients in the combination arm received a higher cumulative doxorubicin dose, possibly explaining some of the improvement. Pending results of the confirmatory phase III trial, doxorubicin plus olaratumab should represent one histology-agnostic first-line treatment.

Elderly/Frail Patients

Elderly and frail patients may be poor candidates for doxorubicin therapy. Pegylated liposomal formulations of doxorubicin typically demonstrate a better toxicity profile compared with unencapsulated doxorubicin. No phase III data exist comparing efficacy equivalency; however, a randomized phase II showed similar outcomes and improved tolerance with liposomal doxorubicin (50 mg/m² every 4 weeks) over standard doxorubicin. Gemcitabine and pazopanib represent viable alternatives.

SELECT HISTOLOGY CONSIDERATIONS

Gemcitabine/Docetaxel

In 2002, gemcitabine/docetaxel demonstrated activity in metastatic leiomyosarcomas, particularly uterine leiomyosarcomas (uLMS). The follow-up SARC002 study supported these findings, but the phase III TAXOGEM study failed to confirm benefit. Nevertheless, gemcitabine/docetaxel emerged as a first-line therapy option for leiomyosarcoma. Recently, the phase III GeDDis trial comparing frontline doxorubicin to gemcitabine/docetaxel in leiomyosarcoma, including uLMS, demonstrated comparable PFS and OS but improved tolerability for doxorubicin. Thus, doxorubicin remains a first-line therapy choice for leiomyosarcoma.

Pazopanib

In 2012, pazopanib, an inhibitor of VEGF receptor and platelet-derived growth factor receptor α and β, became the first and only FDA–approved oral therapy in STS. Anthracycline-pretreated patients (excluding liposarcoma and GIST) randomly assigned to pazopanib versus placebo had a PFS of 4.6 versus 1.6 months, respectively, with benefit across histologies. The ORR and OS were not significantly different between the experimental and control groups.

Trabectedin

Based on several phase II trials, trabectedin was approved in Europe in 2007. FDA approval came in 2015 on the basis of a randomized phase III trial of trabectedin versus dacarbazine in “l-type” sarcomas (liposarcoma and leiomyosarcoma). PFS improved (4.2 vs. 1.5 months, respectively) across histologies, despite the fact that neither ORR nor the primary endpoint of OS were statistically different. However,
trabectedin demonstrated a noteworthy clinical benefit rate (ORR plus stable disease) over dacarbazine (34% vs. 19%), underscoring the importance of disease stabilization as a meaningful endpoint for STS.

**Eribulin**

Eribulin is a unique microtubule inhibitor that achieved its primary endpoint with a modest OS over dacarbazine (13.5 vs. 11.5 months, respectively), but failed to demonstrate a marked PFS improvement in a study of L-type sarcomas. A preplanned subgroup analysis found benefit in liposarcomas but not leiomyosarcomas (median OS: 15.6 vs. 8.4 months, respectively). Eribulin, the first drug to demonstrate liposarcoma-specific OS benefit, was approved in 2016.

**Select Other Histologic Considerations**

Patients with myxoid/round cell liposarcomas typically demonstrate sensitivity to doxorubicin, whereas those with synovial sarcomas are particularly sensitive to ifosfamide. Women with indolent or low-volume uLMS expressing estrogen or progesterone receptor may benefit modestly from aromatase inhibitors, although the magnitude of benefit is uncertain because hormonal expression in uLMS is also prognostic. Unlike virtually all other STS, taxanes are active in angiosarcoma. In contrast, VEGF inhibition via sorafenib and bevacizumab failed to show benefit in these vascular cancers. Recently, cediranib demonstrated PFS benefit over placebo in patients with alveolar soft parts sarcoma. Imitinib has modest activity against pigmented villonodular synovitis/tenosynovial giant cell tumor and metastatic dermatofibrosarcoma protuberans. Perivascular epithelioid cell differentiation is characterized by dysregulated mTOR signaling that responds well to sirolimus. In contrast, clear cell, GIST, and fibromyxoid sarcoma tend to be refractory to most chemotherapy.

**TARGETED THERAPIES**

Although some sarcomas harbor characteristic translocations, with notable exceptions such as perivascular epithelioid cell differentiation and GIST (not further discussed), there are few targetable opportunities. Based on MDM2 and CDK4 coamplification in well-differentiated/dedifferentiated liposarcoma, MDM2 and CDK4/6 inhibitors have been tested with modest efficacy. Molecularrly selective, histology agnostic “basket” trials such as National Cancer Institute MATCH (NCT02465060) and ASCO TAPUR (NCT02693535) are ongoing and may yield relevant information for select diseases. Inhibitors of NTRK fusions, which occur at low rates across cancers, have shown great promise in that unique molecular subset, with 10 out of 11 patients with sarcomas reported responding to NTRK inhibition.

**IMMUNOTHERAPY**

Although foreshadowing the promise of immuno-oncology with Coley toxin, responses to current immunotherapy agents have been mixed across STS. Immune checkpoint blockade has been explored most notably in SARCO28 and ALLIANCE A091401. SARCO28 was an open-label phase II study of pembrolizumab in recurrent/metastatic STS, stratified into four STS cohorts of 10 patients each: undifferentiated pleomorphic sarcoma (UPS), dedifferentiated liposarcoma, synovial sarcoma, and leiomyosarcoma, as well as a separate bone sarcoma cohort. The trial failed to meet the primary response endpoint with an ORR of 18%, but responses were seen in both the STS and bone cohorts. In the STS arm, one patient with UPS experienced a complete response, whereas six patients had partial responses (three UPS, two liposarcoma, and one synovial sarcoma). Thus, the UPS ORR was 40%. Median response lasted 33 weeks, with median PFS and OS of 18 and 49 weeks, respectively. Pembrolizumab was well tolerated with an expected rate of adverse events. PD-L1 expression was low (4% of pretreatment samples) but corresponded with UPS histology and responders. Comparing paired samples, responders trended toward increased cytotoxic T-cell infiltration following treatment.

ALLIANCE A091401 was an 85-patient phase II trial of nivolumab with or without ipilimumab. The ORR of the combination was 16% compared with 5% for nivolumab alone. PFS and OS were improved in the combination arm, with a median PFS of 4.4 versus 2.1 months and OS of 14.3 versus 10.7 months, respectively. Although the combination arm experienced a doubling of grade 3 to 4 treatment-related adverse events (14% vs. 7%), investigators concluded the overall toxicity of each arm was acceptable. Responses across both groups were seen in leiomyosarcoma, myxofibrosarcoma, UPS, and angiosarcoma; expansions in liposarcoma and UPS are planned. The ALLIANCE results underperformed compared with SARCO28, likely due to differences in study design that enriched for UPS in the latter: UPS demonstrates the highest tumor mutational burden, whereas synovial sarcoma has the lowest. Some STS subgroups warrant immediate further investigation, whereas other subgroups will likely require complementary approaches integrating novel immunotherapy.

Cellular therapy trials involving NY-ESO-1, a cancer germ-line antigen expressed by synovial sarcoma, have shown encouraging responses in ongoing CMB305 study for patients (NCT01343043 and NCT02387125).

**CONCLUSION**

Oligometastatic STS encompasses a complex and heterogeneous collection of disease and requires a multidisciplinary approach. Patients with potentially resectable disease and acceptable performance status should be considered for metastasectomy. Although data on metastatic nonpulmonary disease are sparse, extrapolating data from pulmonary literature, there is at least some suggestion for the beneficial role of surgery. Choice of surgical technique is surgeon specific, and minimally invasive techniques such as VATS can achieve results equivalent to traditional thoracotomy. Patients with recurrent pulmonary metastatic disease following initial curative metastasectomy can be considered for repeat surgical resection.
PTA and embolization therapies are minimally invasive, safe, effective, and repeatable treatment options. Image-guided interventional therapies may be performed in conjunction with or as an alternative to other local therapies, including surgery or radiation. Despite limited comparative studies at present, there are convincing data that multimodality treatment of metastatic sarcoma that includes interventional radiology therapies results in improved outcomes and survival.\(^{83}\) Future studies and clinical trials are necessary to refine the role of interventional radiology therapies into the multidisciplinary care of patients with metastatic sarcoma.

Radiotherapy can be safely and effectively delivered to both pulmonary and extrapulmonary metastases. Techniques can include both traditional external beam and SBRT and can result in disease control and palliation. SBRT tends to be well tolerated and potentially equally effective to metastasectomy. Regardless of local modality, careful surveillance is paramount, because the vast majority of patients with oligometastatic disease inevitably will recur. Comparative trials assessing surgery versus interventional radiology versus radiotherapy options are ultimately needed to determine equivalency or superiority of one or another technique; however, such trials are unlikely due to the inherent challenge of randomization to major interventions. Moreover, anatomic and patient selection require individualized, multidisciplinary care plans.

Likely due to the absence of a clear role for adjuvant chemotherapy, STS is often considered chemotherapy resistant, even for intermediate- and high-grade STS. Hopefully, therapeutic nihilism is waning given the multiple new chemotherapies and influx of ongoing clinical trials.\(^{84}\) The rapid accrual of the ALLIANCE A091401 demonstrates that although sarcoma is a rare disease, trials can be completed efficiently. However, it also highlights the need for increased breadth and depth of systemic options. A recent systematic review and meta-analysis of salvage therapy trials (second-line and beyond) in metastatic STS demonstrated a survival benefit to salvage chemotherapy over best supportive care.\(^{85}\) Patients with extensive metastatic STS typically succumb to their disease, but perhaps more than for epithelial cancers, treatment of metastatic STS often remains a multidisciplinary effort, with select patients benefiting from a piecemeal approach that includes local therapy following excellent response to chemotherapy. Ultimately, the optimal approach depends on collaborative management by a team of surgical, orthopedic, radiation, and medical oncologists together with interventional radiologists, all experienced in the management of metastatic STS, balanced against the patient’s disease burden, performance status, and comorbidities.

### References


TUMOR BIOLOGY
Ultimate Precision: Targeting Cancer but Not Normal Self-replication

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OVERVIEW

Self-replication is the engine that drives all biologic evolution, including neoplastic evolution. A key oncotherapy challenge is to target this, the heart of malignancy, while sparing the normal self-replication mandatory for health and life. Self-replication can be demystified: it is activation of replication, the most ancient of cell programs, uncoupled from activation of lineage-differentiation, metazoan programs more recent in origin. The uncoupling can be physiologic, as in normal tissue stem cells, or pathologic, as in cancer. Neoplastic evolution selects to disengage replication from forward-differentiation where intrinsic replication rates are the highest, in committed progenitors that have division times measured in hours versus weeks for tissue stem cells, via partial loss of function in master transcription factors that activate terminal-differentiation programs (e.g., GATA4) or in the coactivators they use for this purpose (e.g., ARID1A). These loss-of-function mutations bias master transcription factor circuits, which normally regulate corepressor versus coactivator recruitment, toward corepressors (e.g., DNMT1) that repress rather than activate terminal-differentiation genes. Pharmacologic inhibition of the corepressors rebalances to coactivator function, activating lineage-differentiation genes that dominantly antagonize MYC (the master transcription factor coordinator of replication) to terminate malignant self-replication. Physiologic self-replication continues, because the master transcription factors in tissue stem cells activate stem cell, not terminal-differentiation programs. Druggable corepressor proteins are thus the barriers between self-replicating cancer cells and the terminal-differentiation fates intended by their master transcription factor content. This final common pathway to oncogenic self-replication, being separate and distinct from the normal, offers the favorable therapeutic indices needed for clinical progress.

Reproduction/self-replication propels all biologic evolution, including neoplastic evolution. Multibillion-dollar public and private efforts have accordingly focused on investigating and targeting cancer self-replication as the heart of malignancy. For meaningful clinical translation, however, normal tissue stem cell self-replication, necessary for a healthy natural lifespan, should be simultaneously spared. The quest can therefore be framed as a search for differences between malignant and normal self-replication that can be used for therapy. Fortunately, such differences have been found, although as a matter of course development of drugs and clinical evaluation have lagged.

REPLICATION AND LINEAGE-DIFFERENTIATION ARE LINKED

Cellular replication, the orchestrated duplication and partitioning of cellular components in all their forms and quantity, is a staggeringly complex process coordinated for millennia by the ancient transcription factor MYC. That is, MYC is a master transcription factor—only a few of the approximately 100 transcription factors expressed in cells are masters—collaborating in combinations to powerfully regulate the expression of other transcription factors and hundreds to thousands of genes. Master transcription factors thereby govern cell fates and functions, illustrated by their remarkable capacity to reverse cells to earlier stages of their ontogeny in a lineage, even into embryonic stem cells or to convert cells of one lineage into another. As canonical a master transcription factor as MYC is, it is nevertheless subordinate to other master transcription factors that activate programs emblematic of metazoan (multicellular) physiology: apoptosis (cell suicide), activated by p53 and its key cofactor p16/CDKN2A, and lineage-differentiation programs (cell specialization), activated by various master transcription factor combinations. Apoptosis dominantly antagonizes MYC to temporarily or permanently prevent cell replication. Lineage-differentiation programs, however, regulate MYC in dramatically different ways depending on the phases of advance of cells along lineage-differentiation axes (Fig. 1).

Tissue Stem Cells

Underpinning tissue homeostasis are stem cells, the cells in normal adult physiology inherently capable of both...
self-replication and multipotency. The self-replication is, however, severely restricted in its rate, certainly as documented for hematopoietic stem cells: upregulation of MYC is limited, intervals between cell divisions extend to weeks or months, and overall proliferation kinetics are quiescent or linear \(^{12,13}\) (reviewed in \(^{15}\)). In fact, the master transcription factor HLF simultaneously produces hematopoietic stem cells and imposes quiescence—knockout of HLF, both increased replication and released forward-differentiation, eventually eliminating the hematopoietic stem cell pool.\(^{17}\)

Transcription factors activating stem cells programs in other tissues have also been shown to concurrently dampen replication: SOX9 in the case of intestinal stem cells\(^{14}\); RBPJ for muscle stem cells\(^{15,16}\); Notch in neural stem cells\(^{17}\); and LHX1 and hair follicle stem cells.\(^{18}\)

Why do stem cell programs go with restricted replication? Stem cells must preserve the integrity of their genomes if they are to replenish tissues through the lifespan of an organism. Although quiescence does not provide complete protection to the genome, replication carries with it additional risks, from mistakes by DNA polymerase, breakage of elongating strands, and from errors in the repair of such damage.\(^ {19}\) The reality and danger of replication errors to physiology is highlighted by inherited defects in repair capacity: DNA double-strand breaks are a form of replication errors, estimated at approximately 10 DNA double-strand breaks per cell cycle.\(^ {20}\) The ataxia telangiectasia–mutated (ATM) gene, which participates in DNA double-strand break repair, is mutated in the germline in ataxia telangiectasia syndrome, producing phenotypes of increased risk for cancers and of premature aging in skin, bones, the small intestine, blood, and the central nervous system.\(^ {21-23}\) Similarly, germline mutations in Fanconi anemia genes that participate in repair of DNA double-strand breaks also produce bone marrow failure, developmental abnormalities, and higher risks for cancers.

If not in tissue stem cells, where then does the volume of replication needed to withstand daily entropy and attrition, estimated at more than 100 billion cells per day, occur?

**Lineage-Committed Progenitors**

Tissue stem cell daughters that commit to differentiate toward specific lineage fates (lineage-committed progenitors, transit-amplifying cells) activate and stabilize MYC to high levels, producing intervals between cell divisions measured in hours\(^ {6,11}\) and exponential growth kinetics (reviewed in \(^{14}\)).\(^ {24-28}\) The biochemical basis for this augmentation of MYC has been shown for myeloid differentiation: master transcription factor drivers of granulomonocytic lineage fates, PU.1, CEBPA, RUNX1, localize at enhancers for MYC\(^ {29}\) and colocalize with MYC at proliferation genes.\(^ {30}\) This partnership produces replications that are rapid in rate but restricted in number because of the eventual activation of terminal-differentiation programs that antagonize MYC and force cell cycle exits (Fig. 1).\(^ {31-38}\)

**Terminally-Differentiated Cells**

These do not actively divide but focus instead on performing the specialized functions needed by the overall multicellular aggregate (Fig. 1).

**DISENGAGING REPLICATION FROM ADVANCES ALONG A LINEAGE**

Hence, oncogenesis necessarily uncouples replication from forward-differentiation, which would otherwise eventually terminate replication. Accordingly, Hansemann, upon the first histologic examinations of cancer in 1890, remarked on “anaplasia” (loss of differentiation) and “dedifferentiation”\(^ {39}\), and, today, clinical pathologists routinely use differentiation-failure to distinguish malignant from benign tumors (e.g., adenocarcinoma from adenoma) and more from less-aggressive transformation (e.g., acute myeloid leukemia [AML]) from myelodysplastic syndromes. Even when loss of differentiation is not obvious by light microscopy, it is evident by gene expression analyses. For example, grade 1 hepatocellular carcinomas, although well-differentiated by light microscopy, demonstrate suppression of hundreds of hepatocyte epithelial-differentiation genes relative to normal liver cells.\(^ {40}\)

At which phase of lineage-differentiation, and how, does oncogenic disengagement of replication from forward-differentiation occur?

**Gain of Function in Tissue Stem Cells (Cancer “Stem” Cell Model)**\(^ {41}\)

Since normal tissue stem cells naturally permit replication without forward-differentiation, gain-of-function events, notionally, RAS mutations that stabilize MYC, or copy number...
gains of MYC\(^{42,43}\) might upregulate replication without triggering forward-differentiation. The caveats are that the gain-of-function mutations must originate in the stem cell compartment, which has been found not to be the case for RAS mutations in AML, since they were detected only in downstream lineage-committed progenitors but not hematopoietic stem cells\(^{44-46}\). Also, this model assumes that high-grade MYC upregulation does not promote forward-differentiation, but, experimentally, MYC introduction into epidermal or hematopoietic stem cells promoted differentiation into epidermal/sebaceous and myeloid lineages, respectively\(^{24,28,47}\).

A variation of this model, proposed for leukemia fusion proteins containing truncated MLL (KMT2A), is that key genes linked with tissue stem cells, e.g., HOXA9, are aberrantly activated in lineage-progenitors, for stem cell–like delinking of replication from forward-differentiation.\(^{48}\) We have found, however, that key HOX genes including HOXA9 are dominantly regulated by lineage-differentiation activating master transcription factors, not vice-versa (HOXA9 does not regulate master transcription factors but is regulated by them).\(^{30}\)

**Loss of Function in Lineage-Committed Progenitors (Cancer-Initiating Cell Model)**

Loss-of-function alterations, such as deletion of coactivators that lineage master transcription factors used to activate terminal-differentiation, might allow replication without forward-differentiation (self-replication) to emerge (Fig. 1).\(^{8,9}\) The guilty genetic alterations may originate, however, in compartments preceding lineage-committed progenitors, e.g., in tissue stem cells or germline, discussed in the “Cell of Origin Versus Cell of Transformation” section.
THE IMPORTANCE OF RECONCILING THESE DIFFERENT MODELS

Conceptual frameworks can profoundly influence selection of hypotheses. As an example, the gain-of-function model, when applied to potently oncogenic MLL (KMT2A) fusion proteins, emphasizes their interactions with coactivators (DOT1L) that might delink replication from forward-differentiation by activating stem cell genes (HOXA9), and, therefore, seeks to inhibit DOT1L. The loss-of-function model looks for ways in which MLL leukemia fusion proteins might, via deletion of the MLL SET domain (the SET domain generates an epigenetic activation mark, H3K4me3), repress terminal-differentiation (Fig. 2), and seeks to inhibit this aberrant repression, e.g., by inhibiting DNA methyltransferase 1 (DNMT1). Starting from the same empirical observations, therefore, different models drive to drugs aiming at quite different molecular targets and goals: inhibiting coactivators to turn genes “off” versus inhibiting corepressors to turn genes “on.”

CELL OF ORIGIN VERSUS CELL OF TRANSFORMATION

To reconcile or choose between these models, examination for the cell-of-origin, the cell in which founding mutations originate (“first hits” in multi-hit oncogenesis) does not provide an automatic answer. RUNX1 loss-of-function mutations in the germline are the most frequent identified cause of familial AML. Cellular expansion and transformation, however, is several commitment decisions removed from the germline cell of origin: in lineage-committed myeloid progenitors via disruption to the PU.1/RUNX1 master transcription factor circuit that normally activates terminal granulomonocytic lineage fates, shown both in vitro and in vivo. Another illustrative example is the recurrent AML mutation DNMT3A-R882H, detected in hematopoietic stem cells in patients’ bone marrows. Despite the mutation, these cells yield normal multilineage hematopoiesis upon engraftment in immune-compromised mice. On the other hand, lineage-progenitors from the same patients’ bone marrows, to which the DNMT3A mutations are propagated, additionally acquire mutations in NPM1 and FLT3 (the most highly recurrent mutations in human AML) and produce leukemic hematopoiesis, wherein the cells replicate without forward-differentiation. As would be expected from these observations, bone marrow replacement in patients with AML is by cells that phenocopy granulocyte-monocyte progenitors. Similarly, germline DNMT3A haploinsufficient and DNMT3A hematopoiesis conditional knockout mice (Mx1-CRE crossed with DNMT3A^{fl/fl}) demonstrate bone marrow and spleen replacement by lineage-committed myeloid progenitors (e.g., granulocyte-monocyte progenitors), accumulating at the expense of hematopoietic stem cells and mature cells. In short, several studies of AML, previously reviewed by us in detail, have indicated that malignant transformation—the emergence of uncontrolled self-replication—occurs in lineage-committed progenitors, remote from germline or stem cell of origin of founder mutations. Is this true of cancer more broadly?

MASTER TRANSCRIPTION FACTOR ALTERATIONS IN CANCER CELLS

Cancers of the same histology, despite profound diversity in genomic alterations, consistently have hundreds of genes similarly suppressed, and similarly upregulated, versus their normal tissue counterparts. Among suppressed genes, there is consistently high representation...
of terminal-differentiation genes, whereas among upregulated genes, there is consistently high representation of replication genes (MYC-target genes). Such broad and consistent programmatic changes suggest altered function of the master transcription factor circuits that regulate the expression of these hundreds of genes. What are the patterns of expression and genetic alteration of these master transcription factors and their key cofactors in cancer?

Master Transcription Factors Expressed by Self-replicating Cancer Cells
Cancer cell lines self-replicate indefinitely ex vivo in plastic bottles and plates, so long as media and conditions meet basic metabolic needs. In cancer cell lines representing the different cancer histologies afflicting humankind, the master transcription factor MYC, or its paralogue MYCN, are consistently highly expressed. Also highly expressed are master transcription factors known to drive tissue lineage-differentiation. This is also true of primary cancer tissues: the master transcription factors expressed resemble those in their normally terminally-differentiated tissue counterparts (Fig. 3). Thus, malignant melanoma cells express high levels of the melanocyte differentiation drivers MITF and SOX10, rhabdomyosarcomas express high levels of the muscle-specifying transcription factor MYOD, clear cell renal cell cancers (RCCs) express very high levels of the renal epithelial-fate driving transcription factors PAX2 and PAX8, hepatocellular carcinomas express very high levels of hepatocyte fate transcription factors FOXA1, FOXA3, and to some extent, GATA4, and AML cells, including AML cells that can overcome interspecies barriers to initiate leukemia in immune-compromised mice (called leukemia “stem” cells or leukemia-initiating cells), express PU.1, CEBPA, and RUNX1 at levels similar to or exceeding those observed in normal terminally-differentiated granulocytes and monocytes, with miniscule levels of hematopoietic stem cell master transcription factors (reviewed in ). Underscoring that such expression is not epi-phenomena, suppression by RNA interference of expressed lineage-differentiation–driving master transcription factors is lethal; cancer cells, being committed to lineage, depend on lineage master transcription factors for their existence.

Master Transcription Factor Alterations in Cancer Cells
Yet, by gene expression analyses, hundreds of target terminal-differentiation genes of these lineage master transcription factors are suppressed, not activated (reviewed in ), suggesting at a minimum, partial loss of function. Accordingly, GATA4 and GATA3, master transcription factors essential for producing several tissue lineages, are haploinsufficient in approximately 50% of all cancers (Fig. 4). RUNX1, CEBPA, RARA, IKZF1, EBF1, and PAX5, necessary for several hematopoietic lineages, are recurrently mutated, deleted, or translocated (reviewed in ) or aberrantly dislocated into cytoplasm in hematopoietic malignancies. It is worth

FIGURE 3. Lineage Master Transcription Factors Expressed in Cancers Are That of Terminally-Differentiated Noncancerous Counterparts

Master transcription factors highly expressed in cancers are that of the corresponding normal differentiated lineage. TCGA Pan-Cancer RNA sequencing. Fifty cases randomly selected for each cancer, and up to 25 of available normals (total 412 cases).

Abbreviations: n, normal tissue; t, tumor tissue.
emphasizing, however, that the loss of function is necessarily partial, since differentiation is a continuum along which all cells exist. Suppression or inactivation of surviving alleles of an expressed lineage master transcription factor circuit is incompatible with cancer cell existence, shown for both liquid53,66-71,75-77 and solid tumor malignancies (Fig. 4).40,72,73

This partial loss of function in differentiation circuits contrasts with biallelic inactivation in approximately 80% of cancers, of TP53 and/or p16/CDKN2A that regulate apoptosis—in common with terminal-differentiation, apoptosis dominantly suppresses MYC-coordinated replication, requiring p53-system inactivation, even as MYC may be simultaneously amplified and stabilized by copy number gains, RAS mutations, PI3K/AKT pathway alterations, etc. (Fig. 4).

The Epigenetic Gradient to Activation of Terminal-Differentiation Genes

Why does partial loss of function in lineage master transcription factor circuits repress terminal-differentiation but spare activation of commitment and replication genes? Using the example of monocyte ontogeny, replication genes (MYC target genes) are already “poised” or “on,” that is, DNA CpG hypomethylated and H3K4me3 enriched, in the earliest tissue precursors, embryonic stem cells to hematopoietic stem cells (Fig. 2). Myeloid commitment genes, although less poised to begin with, interestingly acquire the H3K27me3 repression (“off”) mark rather than the activation mark during monocyte ontogeny (Fig. 2). By contrast, monocyte terminal-differentiation genes undergo substantial chromatin remodeling, to lose CpG methylation marks and increase H3K4me3 marks, during ontogeny, and AML is characterized by a failure of this remodeling (Fig. 2).9,40 Thus, terminal-differentiation genes are particularly vulnerable to loss of chromatin-remodeling function.40,50

Genomic Alterations in the Coactivators Needed to Activate Terminal-Differentiation

Several lineage master transcription factors have been shown to be “pioneers”: they enter chromatin closed to lessor transcription factors, e.g., at terminal-differentiation genes (Fig. 2), and initiate the remodeling needed for access by the basal transcription factor machinery.79 The remodeling work is executed by coactivators (e.g., SWI/SNF) recruited by the transcription factors that use the energy from ATP hydrolysis to move obstructing nucleosomes away from transcription start sites.79 These coactivators are inactivated by deletion and/or mutation in more than 60% of cancers (Fig. 4). Lineage master transcription factors are particular
in the coactivators they use,\textsuperscript{80,81} and, accordingly, different SWI/SNF coactivators are inactivated in different cancers (Fig. 4).\textsuperscript{82} For example, PBRM1 coactivates for the PAX2/PAX8 master transcription factor circuit (our observations in review) that activates the kidney epithelial-differentiation program. \textit{PBRM1} is universally at least haploinsufficient in clear cell RCCs, with biallelic inactivation in approximately 40\% of cases. Additionally, ARID1A coactivates for the GATA4/FOXA1 master transcription factor hub that activates hepatocyte epithelial-differentiation, and \textit{ARID1A} is deleted or mutated (inactivating mutations) in approximately 40\% of HCCs.\textsuperscript{40} Recurrently inactivated coactivators include members of the mediator, splicing, cohesion, and trithorax families (Fig. 5).\textsuperscript{55} Coactivators can also be inactivated indirectly, e.g., gain-of-function mutations in isocitrate dehydrogenases in gliomas and AMLs produce an oncometabolite (R-enantiomer of 2-hydroxyglutarate) that inhibits coactivator components TET2, KDM4A, and KDM4C that use α-ketoglutarate as a cofactor,\textsuperscript{83} and phosphorylation of master transcription factors belonging to the CEBP family, by the RAS and FLT3 pathways that are constitutively activated by oncogenic mutations, has been shown to decrease their coactivator recruitment and repress rather than activate target differentiation genes.\textsuperscript{84,85} 

\textbf{Mathematics}

The tissue compartments in which mutations originate, and the order in which they occur, has been documented for leukemogenesis. The picture painted is that tissue stem cells are crucial for neoplastic evolution since their natural self-replication confers the long lives, high total number of cell divisions, and high volume of progeny (via committed daughter cells) necessary for random, multi-hit neoplastic evolution. For all this, these cells are still only preleukemic. Transformation occurs in lineage-committed daughters to which founding mutations are propagated, shown by (1) master transcription factor expression of cancer cells, (2) the programs consistently suppressed and upregulated versus normal tissue counterparts, (3) surface and gene expression phenotypes of demonstrably self-replicating cells, (4) surface and gene expression phenotypes of cells that accumulate, (5) inactivating mutation and/or haploinsufficiency of lineage master transcription factors and their key coactivators, (6) origin of key transforming mutations (e.g., RAS, NPM1, FLT3 mutations) in lineage-committed progenitors, and (7) the epigenetic gradient to activation of terminal-differentiation but not commitment genes.\textsuperscript{9,41} With intrinsic replication rates naturally so skewed in favor of lineage-progenitors versus tissue stem cells, even small

\begin{figure}
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\includegraphics[width=\textwidth]{figure5.png}
\caption{Corepressor/Coactivator Imbalance in Lineage Master Transcription Factor Hubs Stalls Forward-Differentiation of Inherently Replicative Lineage-Progenitors}
\end{figure}

An empirically observable property of cancers is high expression of lineage master transcription factors, yet anomalously, suppression of terminal-differentiation target genes of these commanders. Transcription factors integrate signaling inputs via dynamic interchange of opposing coactivators and corepressors. Coactivators create the chromatin modifications that facilitate gene activation, whereas corepressors execute the opposite function. A common final pathway of oncogenesis is a shift in coactivator/corepressor stoichiometry at lineage master transcription factor hubs toward corepressors and away from coactivators. Oncogenetically-induced corepressor/coactivator imbalance can be corrected pharmacologically.
advantages here can be amplified tremendously. The corollary is that any advantage accrued to stem cells would have to be massive to compete with normally maximally replicative lineage-progenitors. By way of analogy, committed progenitors are already speeding down the highway and only need to disable the brakes, whereas tissue stem cells sit in the garage with the engine off.

**TARGETING CANCER, BUT NOT NORMAL, SELF-REPLICATION**

Thus, cancer cells are destined for terminal-differentiation by overall master transcription factor content and rely on specific corepressors to forestall these fates and thereby create malignant self-replication (Fig. 5). Inhibiting these corepressors relinks replication to forward-differentiation, activates terminal-differentiation programs, and terminates malignant self-replication (Fig. 5). Since MYC is subservient to terminal-differentiation, replication is terminated even if MYC is stabilized and/or amplified by other genetic alterations typical of cancer including RAS mutations and MYC amplifications. Normal committed progenitors, like the lineage-committed cancer and leukemia cells (including leukemia/cancer “stem” cells), also differentiate. The same treatments increase self-renewal of normal tissue stem cells since these express high levels of master stem cell transcription factors, not differentiation-drivers.

In short, effecting corepressor/coactivator exchange in lineage master transcription factor hubs is sound in the overall genetic and clinical context of cancer.

**Effecting Corepressor/Coactivator Exchange (Specific Clinical Indications)**

The retinoic acid receptor (RARα) exchanges corepressors for coactivators upon binding of its cognate ligand retinoic acid (ATRA), to hence activate granulocyte terminal-differentiation genes. In acute promyelocytic leukemia (APL), the PML gene is fused with RARα to create the fusion protein PML-RARA: physiologic concentrations of ATRA cannot trigger corepressor/coactivator exchange at PML-RARA, and, thus, granulocyte terminal-differentiation genes are repressed instead of activated. Treatment of patients with APL with pharmacologic doses of ATRA, however, forces the corepressor/coactivator exchange and activates granulocyte terminal-differentiation. Arsenic that degrades PML-RARA, via an interaction with PML, also corrects corepressor/coactivator imbalance to activate granulocytic fates. The combination of just these two drugs produces greater than 95% 2-year survival in APL, compared with less than 30% 2-year survival with conventional cytotoxic chemotherapy.

Inhibition of kinases that phosphorylate master transcription factors is another indirect method of actuating corepressor/coactivator exchange and terminal-differentiation, as is inhibition of mutant IDH2 that generates an oncometabolite inhibiting the coactivator components TET2, KDM4A, and KDM4C. We have found that low concentrations of nuclear export inhibitors, sufficient to inhibit mutant-NPM1-mediated nuclear export of the master transcription factor PU.1, restore terminal-differentiation in NPM1-mutated AML cells. These are observations we hope to translate into clinical therapy for chemorefractory disease.

**Inhibiting Corepressors Directly (Multiple Clinical Indications)**

The methods of effecting corepressor/coactivator exchange discussed above are for very specific oncoprogenic contexts. An alternative is to inhibit corepressors directly, an approach that has been scientifically validated for broad application (Fig. 5). The challenge is to develop specific and potent small molecule inhibitors that do not have off-target antimitabolite effects that undermine therapeutic indices.

**DNMT1.** The maintenance methyltransferase and corepressor component DNMT1 is enriched in highly expressed master transcription factor hubs of multiple cancer types and has been scientifically validated as a pan-cancer target (reviewed in; Figs. 4 and 5). The clinical drug decitabine can be administered by dosages and schedules that deplete DNMT1 without cytotoxicity. Noncytotoxic treatments are especially needed to treat myeloid malignancies in elderly patients since the cause of morbidity and death is low blood counts. We therefore treated such patients with a decitabine regimen documented to deplete DNMT1 without cytotoxicity: 0.1 to 0.2 mg/kg per day compared with the U.S. Food and Drug Administration (FDA)–approved 20 to 45 mg/m² per day (a 75%–90% reduction), administered 1 to 3 days/week nonstop to increase probabilities that cancer S-phase entries coincide with drug presence in cells, which is required because DNMT1-depletion by decitabine is S-phase dependent. The treated patients were mostly elderly, and many had disease that was relapsed/refractory to initial treatments. Responses meeting International Working Group criteria occurred in 44% of subjects and were highly durable, with treatment-induced freedom from transfusion lasting a median of 1,025 days. Twenty percent of the subjects were treated for more than 3 years, including several patients older than age 80. Consistent with DNMT1-depletion targeting a final common pathway of transformation, hematologic and cytogenetic responses occurred across the diverse genetic spectrum of disease, including in cases with complex chromosome abnormalities and TP53 mutations. Noncytotoxic DNMT1-depletion was confirmed by serial bone marrow γ-H2AX and DNMT1 analyses. MYC master oncprotein levels were markedly decreased by treatment.

This therapy could not be simply extended to patients with solid tumor malignancies, since decitabine is rapidly deaminated (inactivated) by the enzyme cytidine deaminase (CDA) that is highly expressed in solid tissues (this is why decitabine and other cytidine analogs have severely limited oral bioavailability). CDA upregulation within cancer cells
Histone deacetylases. Histone deacetylases (HDACs) are key components of several multiprotein corepressor complexes. They are also enriched in lineage master transcription factor hubs in cancer cells and have been preclinically validated repeatedly as molecular targets for the induction of terminal-differentiation of liquid and solid tumor cancer cells, with several HDAC inhibitors FDA-approved to treat peripheral T-cell malignancies. Clinical application of HDAC inhibitors has been limited unfortunately by pleiotropic roles of HDACs outside of chromatin, rendering it difficult to separate antimetabolite/cytotoxicity from epigenetic effects; the unintended effects limit achievement of intended epigenetic effect in vivo. Since the side effects reflect the widespread roles of HDAC in normal physiology, it is not immediately clear if this problem will be solved with newer HDAC inhibitors.

Lysine demethylase 1 (KDM1A). KDM1A, a flavine adenine dinucleotide (FAD)-dependent monoamine oxidase, is another corepressor component highly enriched in lineage master transcription factor hubs in cancer cells. Genetic or pharmacologic inhibition of KDM1A has been shown to induce terminal maturation in a number of liquid and solid cancer models. Several KDM1A inhibitors are in clinical trials for cancer indications (EudraCT number: 2013-002447-29; ClinicalTrials.gov identifiers: NCT02177812, NCT02034123, NCT01344707). At least two of the compounds in trials (ORY-1001, GSK2879552) are built around a tranylcypromine warhead that inhibits brain monoamine oxidases that metabolize catecholamine neurotransmitters, a potential source of side effects that might limit realization of intended epigenetic effects.

CHD4 and SMARCA5. Nucleosomes (histone octamers) proximal to gene transcription start sites are physical barriers to gene activation. Reposiing these obstructions is energetically expensive work executed by SWI/SNF or ISWI family chromatin remodeling proteins containing the HEC1c-DExx ATP-ase domain. We have noted enrichment for CHD4 and SMARCA5 containing corepressors in the master transcription factor protein hubs of both liquid and solid cancers, and, therefore, we screened for and identified a drug-like compound series that inhibits the HELICc-DExx domains of SMARCA5 and CHD4 to activate terminal-differentiation in liquid and solid cancer cell lines (unpublished data). Since nucleosome positioning is the crux of the obstruction to gene activation, inhibition of this action could in principle offer corresponding potency.

In sum, validated targets for inhibition have been identified, but there are few drugs for their inhibition, all with limitations (as to be expected). This is a target space crying for new nontoxic drugs.

Resistance

Targeting malignant self-replication is not expected to be curative per se, since all drugs are metabolized, must distribute into all target cells, and successfully engage molecular targets to produce intended molecular pharmacodynamic effects, providing several opportunities for evasion. In other words, resistance must be addressed, perhaps using rational combinations of corepressor targeting drugs, for the worthy aspiration of broadly extending the extraordinary results seen with just two nontoxic drugs in APL.

CONCLUSION

Consistent with corepressor/coactivator imbalance being at the heart of malignant, but not normal, self-replication, effecting corepressor/coactivator exchange indirectly or directly is clinically proven therapy for some indications. In fact, the best overall survival for any disseminated malignancy is for APL treated by this nontoxic modality (approximately 95%). Unleashing the activity of lineage master transcription factors already highly expressed contrasts with the intent of most conventional oncotherapy, which applies stress upstream of p53 in the hope of upregulating it for apoptosis, a toxic and futile intent when p53 is absent/nonfunctional (reviewed in ). In short, actuating corepressor/coactivator exchange releases terminal-differentiation fates intended by the master transcription factors most abundantly contained in self-replicating cancer cells, per the Hippocratic dictum: “Natural forces within us are the true healers of disease.”

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Next-Generation Novel Noninvasive Cancer Molecular Diagnostics Platforms Beyond Tissues

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OVERVIEW

In recent years, there has been a revolutionary expansion in technologic advances and therapeutic innovations in cancer medicine. Cancer diagnostics has begun to move away from a sole dependence on direct tumor tissue biopsy for cancer detection, diagnosis, and treatment monitoring. The need for improvement in molecular cancer diagnostics has never been more important, with not only the advent of cancer genomics and genomics-guided precision medicine but also the recent arrival of cancer immunotherapies. Owing to the practical limitations and risks associated with tissue-based biopsy diagnostics, novel noninvasive cancer diagnostics platforms have continued to evolve and expand in recent years. Examples of these platforms include the liquid biopsy, which is used to interrogate ctDNA or circulating tumor cells, proteomics, metabolomics, and exosomes; the urine biopsy, which is used to assay ctDNAs; saliva and stool biopsies, which are used for molecular genomics assays; and the breath biopsy, which measures volatile organic compounds. These next-generation noninvasive molecular diagnostics assays beyond tissues fundamentally transform the potential utilities of cancer diagnostics to enable repeat, prospective, and serial longitudinal “biopsies” to monitor disease response resistance and progression on therapies. Moreover, they allow continual interrogation and molecular in-depth analysis of the evolving tumor’s pan-canceromics under therapeutic stress. These technological and diagnostic advances have already brought about paradigm-changing next-generation cancer therapeutic strategies to enhance overall treatment efficacies. This article reviews the key noninvasive next-generation molecular diagnostics platforms beyond tissues, with emphasis on clinical utilities and applications.

In recent years, there has been a revolutionary expansion in technologic advances in cancer medicine. For decades, cancer diagnostics has been predominantly dependent on direct tumor tissue biopsy for histologic and pathologic analysis. Modern state-of-the-art next-generation DNA sequencing and genomics bioinformatics analysis have brought forth a new paradigm shift in recent years from microscopic levels of histologic diagnostics to molecular genomics levels of cancer molecular diagnostics. Coupled with the revolution in remarkable drug development innovation and efficiency in the new era of small molecule chemistry and therapeutics, these exciting new trends engendered the birth of genomics-guided personalized cancer therapy, with examples of inhibitors adopted in the treatment of EGFR-mutant,1 and ALK-fusion lung cancer,2 and BRAF-mutant melanoma,3 among others. Nonetheless, with the current widespread clinical applications of genomics-matching personalized cancer therapy, it has also become increasingly evident that the need to obtain a large amount of tumor tissue through invasive tumor-needle or surgical biopsy procedures is self-defeating. The risks and inconvenience of such invasive procedures limit the scope of molecular-genomic profiling achievable in the tissues. This problem is substantially compounded by the arrival of cancer immunotherapies in the last few years, for which the need for diagnostics and predictive biomarkers is paramount. As a result, many research studies have been emphasized in achieving next-generation novel cancer diagnostics beyond the use of tumor tissues obtained from primary or metastatic tumor sites. These include the innovative utility of various body fluids or substrates from different body compartments that allow more noninvasive and low-risk access. In this article, we provide a broad overview of the emerging or well-developed technologic platforms (Fig. 1) for these novel cancer diagnostic applications.

LIQUID BIOPSY

Cellular Compartment

Circulating tumor cells. Circulating tumor cells (CTCs) are cells that have disseminated away from the primary tumor or secondarily from metastatic sites and further deposited into the circulatory bloodstream.4-6 Previous studies
suggested that epithelial-to-mesenchymal transition (EMT) may be involved in this active mobilization and dissemination of tumor cells, increasing their plasticity and transmigratory potential.\(^7\),\(^8\) EMT is thought to assist tumor cells in their active intravasation mechanisms into the vasculature. During this process of dissemination, epithelial tumor cells lose their cell-cell contact and apical-basal polarity to gain a more elongated cell phenotype associated with enhanced cell motility and invasiveness.\(^9\),\(^10\) Interestingly, recent evidence also suggests that platelets adhering to CTCs in the circulation could induce EMT itself.\(^11\) The EMT activation process leading to a more motile and invasive phenotype is also induced by the milieu of the tumoral microenvironmental make-up.\(^12\) EMT-triggering signals include transforming growth factor β secreted by the activating platelets,\(^11\) integrin-macrophage interactions through epidermal growth factor supply,\(^13\) and proinflammatory cytokines secreted by fibroblasts.\(^4\),\(^14\)

**Circulating tumor cell enrichment and detection.** Because CTCs clearly represent the tumor cell populations responsible for and involved in the process of metastasis, which is the leading cause of cancer morbidity and mortality, there has been intense interest in enhancing the ability to enrich, capture, detect, isolate, and characterize CTCs. Nonetheless, there are numerous intrinsic challenges in this approach. The size dimension of CTCs varies depending on the different cancer types of origin; for example, small cell lung cancer (SCLC) cells are only approximately 10 μm in diameter, but prostate CTCs can be larger than 100 μm.\(^15\) Moreover, CTCs are extremely rare, and the sensitivity of CTC detection in patient blood is highly dependent on detection methods. No validated formula is available to estimate the true number of CTCs for each patient with cancer, or even for any cancer type. Importantly, how to define what constitutes a CTC and whether even the detected CTCs are functionally important is also quite controversial and challenging. It was recently suggested that even EMT in the CTCs belongs to a continuum rather than a binary phenotype.

**CellSearch** (Menarini Silicon Biosystems Inc., San Diego, CA) is currently the only U.S. Food and Drug Administration–approved detection system for enrichment, detection, and enumeration of CTCs, based on the epithelium-specific cell adhesion molecule (EpCAM) expressed on the surfaces of epithelium-derived CTCs. Allard et al\(^16\) reported average recovery sensitivity of 85% or greater. Beyond enumeration, which obviously has limitations in the underlying biologic information and applications to induce wide clinical adoption, newer approaches to achieve CTC capture have been developed, including microfluidic platforms such as the

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**FIGURE 1. Novel Noninvasive Cancer Molecular Diagnostics Platforms Beyond Tissues**

Abbreviations: CTC, circulating tumor cell; cfDNA, cell-free DNA; VOC, volatile organic compound; CSF, cerebral spinal fluid.
CTC-Chip, in which CTCs interact with EpCAM-coated micro-posts under laminar flow conditions. However, despite a more streamlined workflow, this positive-selection capture platform and other similar available platforms still depend on EpCAM detection, which may not best define a bona fide CTC. To overcome the challenge of CTCs possessing the EMT phenotype and potentially having low to negative EpCAM expression, a number of studies have pioneered the use of EpCAM-independent enrichment strategies. Examples include using CD45-conjugated magnetic beads to enrich CTCs through leukocyte depletion by the EasySep bi-antibody leukocyte depletion kit (STEMCELL Technologies, Vancouver, BC, Canada) in an negative electromagnetic separation.

Another novel platform that has emerged recently is the VTX-1 liquid biopsy system (Vortex Biosciences, Menlo Park, CA), which is capable of capturing and isolating CTCs that may remain viable and requires no preprocessing or labeling of blood samples. Sollier et al reported using this system to extract and enumerate CTCs from the blood of patients with lung cancer (23–317 CTCs/7.5 mL) and breast cancer (25–51 CTCs/7.5 mL) and lung cancer.

By using these new technologies to fully interrogate CTCs molecularly or genomically, one could further unleash the power of the molecular diagnostics platform with multitudes of possible clinical applications. Fan et al demonstrated high sensitivity and specificity in hepatocellular cancer diagnosis using CTCs and could apply them as a real-time parameter for risk prediction and treatment monitoring, enabling early decision making to tailor effective antitumor strategies. Miyamoto et al used microfluidic cell enrichment to establish a sensitive and high-throughput strategy for analyzing prostate CTCs and reported its potential utility in guiding treatment selection in both metastatic and localized prostate cancer. Wang et al combined a postsurgical quantity of small triploid CTCs (five or more cells per 6 mL blood) and multiploid (pentasomy of eight or greater) circulating tumor stem cells (CTSCs) or circulating tumor microembolism (CTMs; either one or more than one), which correlated with poor prognosis for patients with hepatocellular carcinoma and helped predict recurrence. Ilie et al collected peripheral blood samples with CTCs and circulating white blood cells from 106 patients with advanced non–small cell lung cancer (NSCLC). The authors demonstrated that PD-L1 status in CTCs and circulating white blood cells correlates with PD-L1 status in tumor tissue, revealing the potential of CTC assessment as a noninvasive real-time biopsy to evaluate PD-L1 expression for patients with advanced-stage NSCLC.

A recent prospective study to evaluate CTC profiles in NSCLC molecular subgroups enrolled 125 patients with stage IIIb to IV NSCLC without treatment. Of these patients, 51 (40.8%) were found to betotal CTC-positive and 26 (20.8%) were vimentin CTC-positive at baseline. Multivariate analysis showed that patients with five or more total CTCs had reduced overall survival compared with patients with fewer than five total CTCs. The baseline presence of five or more total CTCs was validated to be correlated with a poor prognosis. CTCs from patients with EGFR-mutant NSCLC expressed EMT characteristics not seen in CTCs from patients with KRAS-mutant adenocarcinoma.

Ilie et al adopted the CellSearch and ISET (Rarecells, Paris, France) technologies to enrich patients with advanced stage III/IV NSCLC and to interrogate MET biomarker expression. With CellSearch, CTCs were found for 83 of 256 patients (32%). With ISET, CTCs were found for 80 of 106 patients (75%). MET expression was found on ISET CTCs in 72% of cases, whereas MET expression on matched-patient tissue was positive for 65% of patients (93% concordance). Quantitative MET expression analysis using H-scores revealed a strong correlation of MET expression between tissue and CTCs (Spearman correlation, 0.93). The study results identified CTCs as a potential method for noninvasive, real-time biopsy to determine the MET status of patients entering clinical trials.

Real-time prospective CTC measurement is an attractive platform to monitor disease treatment response and progression. In a recent study, Pailler et al collected blood samples at baseline pretreatment and 2 months after crizotinib treatment from 39 patients with ALK-fusion NSCLC undergoing crizotinib therapy. The results suggested that the dynamic change in CTC numbers with ALK-copy number gain may be a predictive biomarker for crizotinib efficacy, lending further support for serial molecular analysis of CTCs as a promising method for real-time therapy monitoring and clinical outcome prediction for these patient populations.

### Soluble Compartment

**ctDNA.** Both cell-free DNA (cfDNA) and ctDNA originating from normal and cancer cells can be identified and isolated in the peripheral blood. The major fragment size of cfDNA is approximately 170 base pairs, which corresponds well to the nucleosomal fragments resulting from the process of cellular apoptosis. ctDNA is a fraction of cfDNA that originates from primary, metastatic tumors in the body or from CTCs themselves. As a result, ctDNA fragments are found to contain tumor-specific somatic alterations and epigenetic aberrations in the blood. The estimated half-life of free DNA in the circulation is reported to be between 16 minutes and 2.5 hours. Nonmutant cfDNA molecules are longer than ctDNA in plasma.

The detection of ctDNA for molecular diagnostics is fundamentally challenged by the large excess of background wild-type DNA present in the circulation. Tumor-specific markers that allow the distinction of tumor-derived ctDNA as ctDNA from the wild-type DNA fraction can include mutations, indels, gene copy number changes, chromosomal rearrangements, or aberrant methylation. Levels of wild-type DNA can be released during serum preparation; hence, plasma is preferred as the biologic material for molecular extraction and assays. Chromosomal rearrangements can be detected with high sensitivity using polymerase chain reaction (PCR) but require genome-wide sequencing of the primary tumor to find potential target aberrations. Copy number changes detected by low-coverage genome sequencing have been
applied to detect ctDNA without knowledge about the primary tumor genome, but this approach requires relatively high ctDNA concentrations for a successful detection.\textsuperscript{38} Point mutations and indels (short insertions and deletions) are the most frequently used diagnostic ctDNA markers.\textsuperscript{31} Studies have shown reasonably good concordance of tumoral genomic alterations in ctDNA compared with that detected from tumor tissue genomic assays.\textsuperscript{39} However, there are also studies that highlight the high specificity of ctDNA mutation detection but low sensitivity compared with tumor tissue mutation assays, suggesting that negative ctDNA assays might need to be confirmed with tumor tissue DNA mutation detection, as in the case of the \textit{EGFR-T790M} assay.\textsuperscript{40-43}

Liquid biopsy techniques for assaying ctDNAs for genetic/genomic marker alterations have been increasingly applied in recent years to longitudinally monitor patients with cancer,\textsuperscript{44-48} especially those with initial actionable genomic mutations/alterations who are receiving specific cancer therapies. To detect ALK fusions and ALK mutations and track the evolution of drug resistance during treatment, Dagogo-Jack et al\textsuperscript{45} procured blood plasma from 22 patients who had ALK-positive disease with acquired resistance to ALK tyrosine kinase inhibitors (TKIs). The correlation between plasma ALK mutations and response to distinct ALK precision inhibitors brought attention to the potential for liquid ctDNA biopsy analysis to guide ALK precision therapy decisions.\textsuperscript{45} In another recent study, Guibert et al\textsuperscript{46} collected 168 specimens from a total of 46 patients with NSCLC and adopted enhanced tagged amplicon sequencing of hotspots 168 specimens from a total of 46 patients with NSCLC and adopted enhanced tagged amplicon sequencing of hotspots for ctDNA-driven therapeudic studies.\textsuperscript{49} Most recently, a new liquid biopsy assay platform, CancerSEEK, sought to detect eight common types of cancer (i.e., esophagus, breast, lung, stomach, liver, pancreas, colorectum, and ovary) through assessment of the levels of circulating proteins and mutations in cfDNA.\textsuperscript{50,51} The authors reported a positive result of about 70\% (median) across the eight common cancer types among more than 1,000 patients. The specificity was greater than 99\%, and only 7 of 812 healthy controls had a positive score on the CancerSEEK test. Currently, there are numerous active ongoing clinical studies investigating the utilities of CTCs and cfDNA/ctDNA in human cancers (Table 1).

**Blood proteomics.** Beyond DNA in the blood compartment, soluble protein and peptides represent other biomolecular analytes that can be measured for clinical diagnostics purposes. Technologically, it is more difficult to identify and measure individual protein peptides beyond proteomics profiling for peptide signatures, compared with the genomics platforms. As a result, advances in liquid proteomics biopsies trail behind liquid genomics, especially the ctDNA biopsy for clinical/translational applications. Nonetheless, steady progress has been made in this area over the past 1 to 2 decades.

Blood-based proteomic biomarker assays have recently met with notable milestones in bedside adoption. A blood-based proteomics biomarker signature test, VeriStrat (Biodesix, Boulder, CO), was developed using matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MS)\textsuperscript{52-54} for patients with wild-type \textit{EGFR} lung cancer to stratify them into a “good signature” group and a “poor signature” group. Patients with a good signature are predicted to potentially derive benefits from platinum-based chemotherapy, single-agent chemotherapy, or \textit{EGFR-TKI} therapy. Conversely, patients with a poor signature are predicted to be less likely to respond to platinum-based therapy and single-agent chemotherapy and not likely to respond to \textit{EGFR-TKI}. A phase III study to test the predictive power of the VeriStrat test in the second-line therapy of patients with advanced NSCLC was published in 2014.\textsuperscript{54} The investigators analyzed 129 patients (91\%) randomly assigned to the chemotherapy treatment group and 134 patients...
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<td>NCT03312374</td>
<td>ctDNA as a prognostic marker for postoperative relapse in early- and intermediate-stage colorectal cancer</td>
<td>Sun Yat-sen University, China</td>
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<td>NCT03302325</td>
<td>ctDNA as a liquid biopsy for patients with stage IV solid tumors</td>
<td>Medical University of South Carolina, United States</td>
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<td>NCT03115138</td>
<td>Evaluation of ctDNA as a theranostic marker in the management of glioblastomas</td>
<td>Centre Hospitalier Universitaire, Amiens, France</td>
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<td>NCT03214991</td>
<td>Usefulness of ctDNA as a prognostic factor in pancreatic cancer</td>
<td>Ji Kon Ryu, Korea</td>
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**TABLE 1. Ongoing ctDNA and CTC Clinical Trials From 2017**

**ctDNA**

**Lung cancer**

**Breast cancer**

**Colorectal cancer**

**Other tumors**

**CTC**

**Prostate cancer**

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Continued
(94%) randomly assigned to the erlotinib treatment group. A significant interaction between treatment and proteomic classification was found. Patients with a poor VeriStrat serum protein test classification had worse survival with erlotinib than chemotherapy (HR 1.72; 95% CI, 1.08–2.74; p = .022). There was no overall survival difference between treatments for patients with a good proteomic test classification. The authors concluded that VeriStrat serum protein test status is predictive of differential benefit in overall survival for erlotinib versus chemotherapy in the second-line setting. Patients classified as likely to have a poor signature had better outcomes with chemotherapy than erlotinib.

More recently, the VeriStrat serum protein test was evaluated among patients with advanced squamous cell NSCLC treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study of 795 patients.55 Pretreatment VeriStrat status was correlated with overall survival, progression-free survival, and other endpoints. The investigators found that a good VeriStrat classification was strongly associated with favorable outcomes with either afatinib or erlotinib compared with a poor VeriStrat classification. Multivariate analysis showed that VeriStrat was an independent predictor of overall survival for afatinib-treated patients, regardless of Eastern Cooperative Oncology Group performance status or best response to first-line chemotherapy. For patients with a good VeriStrat classification, survival outcomes were found to be better with afatinib treatment (HR 0.79; 95% CI, 0.63–0.98) than with erlotinib treatment. A recent questionnaire study reported that the serum-based proteomic test impacted treatment recommendations among physicians ordering the VeriStrat test.56

**Blood metabolomics.** Although the development of molecular cancer diagnostics has been emphasized in the fields of genomics, transcriptomics, and proteomics in the past decade, there is renewed recognition and dedicated research effort in the area of cancer metabolism and metabolomics. With advances in and wider adoption of MS-based profiling technology, blood serum or plasma-based metabolite measurements can now be readily achieved, both in targeted individual metabolite measurement and in global metabolomics profiling. A number of studies focusing on blood-based metabolite assays for lung cancer diagnostics have been published over the past decade.57-63 Nonetheless, the platforms studied primarily remain investigative in nature and are not yet ready for clinical applications. Prospective validation studies are mostly still lacking. Various studies have also produced differing and sometimes conflicting metabolite identities and/or quantities, probably at least partly as a result of methodologic and instrumentation differences, making it difficult to draw more sound conclusions on the platform’s utility. A deeper understanding of and insight into the interrelationship between normal and cancer metabolic pathways and the correlations with metabolites produced would certainly help the interpretation of future cancer metabolites/metabolomics biomarker research.

With the advances in MS instrumentation and computational bioinformatics methods, there has been a steep increase in literature reports in recent years on the use of blood-based global metabolomics profiling in various human cancers, ranging from cancer risk evaluation,64 diagnostics for genotype-phenotype (e.g., BRCA1-mutated breast cancer),65 early cancer detection,66,67 and surveillance of cancer recurrence/progression.68

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**TABLE 1. Ongoing ctDNA and CTC Clinical Trials From 2017 (Cont’d)**

<table>
<thead>
<tr>
<th>ClinicalTrials.gov Identifier</th>
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<td>NCT03327662</td>
<td>Utilizing CTC counts to optimize systemic therapy of metastatic prostate cancer</td>
<td>Institute of Cancer Research, United Kingdom</td>
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<td>NCT03070002</td>
<td>Phase II study to evaluate denosumab in ER- and/or PR-positive, HER2-negative metastatic breast cancer with bone metastases and detectable CTCs</td>
<td>Northwestern University, United States</td>
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<td>NCT03213041</td>
<td>Phase II study to evaluate the impact on PFS with combination carboplatin/pembrolizumab for patients with CTC-positive, HER2-negative metastatic breast cancer previously treated with anthracyclines and taxanes</td>
<td>Northwestern University, United States</td>
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<td>NCT03032913</td>
<td>Diagnostic accuracy of CTCs and onco-exosome quantification in the diagnosis of pancreatic cancer</td>
<td>University Hospital, Bordeaux, France</td>
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<td>NCT03033927</td>
<td>CTC and tumor tissue models for predicting effective pancreatic cancer response</td>
<td>Memorial Sloan Kettering Cancer Center, United States</td>
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<tr>
<td>NCT03295591</td>
<td>CTC enumeration and clinical factors in metastatic colorectal cancer for liver resection</td>
<td>University of Hong Kong, Hong Kong</td>
</tr>
<tr>
<td>NCT03162198</td>
<td>Frequency of CTCs and amount of cfDNA for patients with cirrhosis with hepatocellular carcinoma</td>
<td>Institute of Liver and Biliary Sciences, India</td>
</tr>
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</table>

Abbreviations: CTC, circulating tumor cell; NSCLC, non–small cell lung cancer; UMI, unique molecular identifier; NGS, next-generation sequencing; EBUS-TBNA, endobronchial ultrasound-guided transbronchial needle aspiration; ER, estrogen receptor; PR, progesterone receptor; PFS, progression-free survival.
SALIVA BIOPSY

The utility of DNA extracted from saliva samples for genome-wide molecular research platforms has been studied and found to be feasible, especially compared with blood DNA. A recent pilot study showed that a salivary DNA tumor-suppressor methylation gene panel could have the potential to detect early-stage tumors for patients with HPV-negative head and neck squamous cell carcinoma. Methylation levels of patients with HPV-positive head and neck squamous cell carcinoma were deregulated by HPV infection.

In 2014, a novel platform of electric field–induced release and measurement was developed to detect EGFR mutations directly in body fluids with a multiplexable electrochemical sensor. The investigators demonstrated that EGFR mutations could be detected in the saliva of patients with NSCLC, with an area under the curve of 0.94 for Del19 and 0.90 for L858R. In 2016, Pu et al used electric field–induced release and measurement and detected the classic oncogenic EGFR mutations in the saliva plasma ctDNA samples of 17 patients with lung adenocarcinoma. They reported complete concordance of the assay results, with an area under the curve of 1.0.

CEREBROSPINAL FLUID BIOPSY

The brain and the central nervous system (CNS) represent a sanctuary where tumor cells residing there could be protected from systemic therapy due to the blood-brain barrier as a therapeutic obstacle. Similarly, ctDNA from primary CNS tumors is rarely detected in the systemic blood circulation, unlike in other visceral primary solid tumors. Hence, the cerebrospinal fluid (CSF) compartment represents a unique and potentially highly informative space for molecular diagnostics development.

In 2006, Choong et al identified CTCs in the CSF of a patient with lung cancer with advanced EGFR-mutant disease and symptomatic leptomeningeal metastases that had progressed during therapy. They further demonstrated the feasibility of detecting a unique EGFR gene mutation (E884K) in the laser-capture microdissected CSF CTCs responsible for drug resistance against erlotinib but hypersensitization to gefitinib. In addition, CSF ctDNA from patients with cancer was adopted for quantitative detection of cancer gene mutations using digital PCR and targeted amplicon sequencing methods, compared with collected plasma, for seven patients with solid brain tumors. The authors identified seven somatic mutations from the CSF of a patient with leptomeningeal disease through the use of cancer panel sequencing, which was also in concordance with genotype testing on the corresponding primary tumor biopsy.

More recently, Pentsova et al used NGS of 341 cancer-associated genes in the CSF of 53 patients with known or suspected CNS metastatic disease from solid malignancies. They reported detection of somatic genomic alterations for 63% (20 of 32) of patients with solid tumor CNS metastases, 50% (6 of 12) of patients with primary brain tumors, and 0% (0 of 9) of patients without CNS involvement by cancer. CSF tumor-associated cfDNA was also detected from primary CNS tumors (medulloblastomas, ependymomas, and high-grade gliomas) abutting a CSF space or cortical surface.

A recent study showed that the sensitivity of comprehensive NGS for somatic mutation detection of the CNS ctDNA was higher than that using plasma ctDNA for patients with CNS tumors (58% vs. 0%). For patients with abundant visceral disease, the sensitivity of CNS DNA and plasma DNA was comparable (60.5% vs. 55.5%). Moreover, the results also showed that the CSF ctDNA derived from CNS tumors was more abundant than that in the plasma. Importantly, the authors further demonstrated that CSF ctDNA levels fluctuated longitudinally in a time-dependent and in parallel fashion mirroring the changes in brain tumor burden. In another recent study, Li et al detected CSF-associated ctDNA using droplet digital PCR for a patient with BRAF-V600E-positive melanoma to monitor the response of metastatic leptomeningeal disease treated with whole brain radiotherapy and BRAF-specific inhibitors. Using nine CSF samples over 6 months, the mutant CSF ctDNA fractions were found to match well with the disease burden and clinical course under treatment, and they corresponded well with the treatment response. Whole-exome sequencing (WES) revealed a canonical cancer gene mutation, PTEN-R130*, in CSF ctDNA of a patient with leptomeningeal disease both before treatment response and after disease relapse.

In addition, similar mutational profiles were found in the cellular and ctDNA (cfDNA), supporting the notion that the ctDNA is a derivative and representative of leptomeningeal disease cells. Hence, CSF ctDNA represents a novel molecular diagnostics platform for use as (1) a method for genomic biomarkers and actionable mutation detection, (2) a complementary tool to diagnose CNS tumors and leptomeningeal carcinomatosis, and (3) a monitoring tool for disease burden and treatment progress in CNS malignancies.

URINE BIOPSY

Urine is an attractive body fluid compartment for cfDNA molecular assays for cancer diagnostics. The urine biopsy is truly noninvasive, without even the need for a needle phlebotomy as in the case of a blood biopsy. Patients can collect their own urine samples at home or in the hospital or clinic. Furthermore, serial sample collection is not difficult or risky for patients and is usually not restricted by patient performance status or disease conditions. Attempts to achieve molecular diagnostics in urine samples for genitourinary cancers date back decades. In 1991, p53 gene mutations were first identified in the urine sediment of patients with bladder cancer. Subsequently, a number of reports followed that demonstrated various gene mutations (e.g., FGFR mutations) identified in the urinary ctDNA extracted from patients with genitourinary cancer. Besides gene mutations, urine can be used as a source for epigenetic alteration assays. In 1989, a three-marker DNA hyper- and hypomethylation panel (IRAK3, L1-MET, and SOX1) in urine sediment was reported to accurately predict bladder cancer recurrence among 80% of patients, which compared
favorably to urine cytology (35%) and cystoscopy (15%).

Today, it is understood that there are two different fractions of ctDNA in the urine. First, ctDNA can be derived from the urinary tract and associated endothelial cells as high molecular weight DNA. Second, ctDNA can be originated as low molecular weight DNA from ctDNA fragments that were excreted into urine during the process of renal glomerular filtration. Studies recently reported that urinary ctDNA can be detected in nonurothelial cancers as well, such as in liver cancer with TP53 mutations and in NSCLC with EGFR mutations.

One of the challenges in urinary ctDNA molecular detection and diagnostic assays is related to the fact that not only is urinary ctDNA highly fragmented but it is also present with a very low abundance (< 0.01%) among the background of wild-type ctDNA. This is similar to the technical challenges experienced in the field of plasma-based blood biopsy molecular assays. Despite these technical difficulties, a sensitive and quantitative detection of EGFR, BRAF, and KRAS mutations in urine was reported to be achievable using short-footprint mutation enrichment PCR coupled with an NGS approach. Using this platform, reported limits of detection for EGFR mutations L858R, Del19, and T790M in urine or plasma were 0.006%, 0.006%, and 0.01%, respectively, which compare favorably with the U.S. Food and Drug Administration-approved Cobas EGFR Mutation Test (limit of detection ≥ 0.2%; Roche Molecular Diagnostics, Pleasanton, CA).

Chen et al reported dynamic tracking of EGFR mutations among patients with NSCLC using urinary ctDNA detection in a serial monitoring trial of patients receiving precision TKIs. Their results showed a concordance in the quantity of urinary ctDNA and plasma cfDNA at baseline as well as in ctDNA decline during treatment. Using the short-footprint mutation enrichment NGS assay, Reckamp et al reported detection of oncogenic EGFR mutations and T790M resistance mutation in the urine and plasma of patients with NSCLC with comparable sensitivity. The group retrospectively analyzed samples from 63 patients with advanced NSCLC enrolled in TIGER-X, a phase I/II study of rociletinib (a third-generation EGFR-TKI) focusing on the most common, recurrent EGFR hotspot mutations, using the mutation enrichment PCR/NGS platform. The sensitivity of EGFR mutation detection in urine was up to 80% to 93% in samples that met recommended urine volumes (90–100 mL). A high specificity of 94% to 100% was attained with the EGFR urine testing assay, as determined using samples from healthy volunteers. Further evaluation of the concordance between urine and tissue EGFR T790M results in an expanded data set yielded a somewhat improved positive percentage agreement of 81% and equivalence in the rate of detection compared with plasma. The negative percentage agreement was 31%, raising the issue of discrepancies between tissue and liquid biopsy results likely as a result of tumor sampling errors and intratumoral heterogeneity. Recently, some investigators proposed a patient treatment paradigm in EGFR-mutant NSCLC, in which plasma genotyping serves as the reflex test upon progression on first-generation EGFR-TKIs to ameliorate the challenges associated with repeat tumor tissue biopsies. A negative ctDNA assay result would prompt tumor tissue rebiopsy and genotyping. Most recent data on the clinical relevance and validity of urine ctDNA molecular testing suggest that it could be included in the molecular diagnostics model to combine urine- and plasma-based genotyping assays to precede tumor tissue biopsies.

STOOL BIOPSY

Potential use of stool samples for molecular detection of colorectal cancers has long been sought as a means to achieve early detection of malignancies. Reports of detecting oncogenes in patient stool samples date back to 1992, when Sidransky et al identified RAS oncogene mutations in the stool of patients with curable-stage colorectal cancer. KRAS represents one of the most well-known and well-characterized oncogenes in human cancers, which can be somatically mutated within several hotspots (codons 12, 13, and 61) in a variety of cancer types. As such, much effort has centered on achieving early cancer detection by assaying for the presence of KRAS mutations in human tumors such as those in the colon, rectum, lung, and pancreas. Besides stool samples, molecular diagnostics tests using mutated KRAS detection have been reported in pancreatic and duodenal lavage fluid, sputum, and lavage samples from patients with colorectal and lung cancers. In addition to KRAS, early studies have also detected adenomatous polyposis coli mutations in stool DNA from patients with colorectal tumors, raising the promise for noninvasive early detection of the disease. Both proximal and distal colorectal cancers can be well detected similarly using stool DNA molecular assays.

Although colonoscopy screening is proven to be effective in the early detection of colorectal cancer and to impact survival rates, target population compliance remains low, partly because of the invasive and unpleasant nature of the procedure. Stool DNA detection has been found to notably improve sensitivity compared with fecal occult blood tests. Compared with colonoscopy screening, stool DNA detection is quite attractive because of its noninvasive and convenient nature. In 2014, the U.S. Food and Drug Administration approved Cologuard (Exact Sciences Corp., Madison, WI), a multitarget stool DNA test for colorectal cancer screening for average-risk adults age 50 and older. The interval testing frequency was determined to be every 3 years with adequate Medicare coverage. Effective July 1, 2017, United Healthcare began covering Cologuard as a colon cancer screening test. Cologuard incorporates molecular assays for aberrantly methylated BMP3 and NDRG4 gene promoter regions, mutant KRAS, and β-actin as well as an immunochromatographic assay for human hemoglobin. Cologuard is based on a study by Imperiale et al, which demonstrated notably improved sensitivity for colorectal cancer detection compared with the fecal immunochemical test. Although Cologuard is a one-time screening stool DNA test that detects 92% of cases of colorectal cancer among asymptomatic average-risk persons compared with 74% with the fecal immunochemical test, Cologuard was able to detect less than one-half of
advanced precancerous lesions (42% sensitivity) and produced a substantial number of false-positive results.

Further molecular testing methods are in development to improve the detection of epigenetic changes (e.g., DNA methylation in plasma and stool DNA samples). Li et al.97 developed a methyl-BEAMing (Beads, Emulsion, Amplification, Magnetics-ing) technology to enable absolute quantification of the number of methylated molecules in a biologic sample, achieving highly sensitive enumeration of as few as 1 methylated molecule in approximately 5,000 unmethylated molecules in DNA from plasma or stool samples. Digital quantification of rare methylation events in clinical samples could have translational applications in cancer diagnostic and prognostic uses as well as in preclinical evaluation of novel epigenetic biomarkers.

EMERGING NEW PLATFORMS
Liquid Biopsy

Exosome profiling. Peripheral blood exosome (microvesicle) profiling is an area of exciting and potentially impactful liquid biopsy research that has emerged in recent years. Exosomes were first described in 1983 by Pan and Johnstone98 as a subclass of extracellular nonvesicles with a 40- to 150-nm diameter membrane with an endocytic origin that contain biomolecules of nucleic acids (including DNA, mRNAs, and microRNAs), proteins, and lipids and nucleic acids that are released by all cell types, including cancer cells. Exosomes are believed to be involved in intercellular communication in physiologic and malignant conditions. Cancerous exosomes carry a cargo load of malignant bioinformation in the form of nucleic acids, proteins, and lipids that are capable of reprogramming the recipient cells. Recently, exosomes have been highlighted as putative transforming agents in malignancies, having a potentially causative role in major steps or processes of tumor progression, including immune response modulation, tumor microenvironment reprogramming, invasion, and metastasis.99,103

Of interest, recent studies suggested that exosomal miRNAs may be involved in disease progression, potentially via stimulating angiogenesis and promoting metastasis.104 Most recently, another new study demonstrated for the first time that before tumor cells acquire metastatic capacity, the tumors alert the host immune system continuously by generating exosomes, which carry triggers of innate immune responses such as the reported pigment epithelium-derived factor.105 Another recent study106 demonstrated that certain microRNAs (e.g., miR-196a and miR-1246) are specifically enriched in pancreatic cancer cell-derived exosomes and are present in the plasma exosome at elevated levels among patients with localized pancreatic cancer. Fang et al.107 recently reported that tumor-derived exosomal miR-1247-3p showed positive correlation with lung metastasis for patients with hepatocellular carcinoma and could convert fibroblasts to cancer-associated fibroblasts by decreasing B4GALTL3, which would then activate the β1-integrin/nuclear factor-kB signaling pathway in the lung premetastatic niche from hepatocellular cancer. Furthermore, cancer-associated fibroblasts displayed increased secretion of interleukin-6 and interleukin-8, resulting in the promotion of cancer stemness, EMT, chemoresistance, and tumorigenicity of tumor cells. Most recently, a novel liquid biopsy platform that can achieve immense coverage of system-wide, native biomolecules was developed for plasma exome profiling for patients with cancer using a next-generation systems biology approach.108 Domenyuk et al.108 used this novel approach (named adaptive dynamic artificial poly-ligand targeting, which embodies an enriched library of single-stranded oligodeoxynucleotides to profile complex biologic samples) as a highly specific profiling tool to distinguish women with or without breast cancer based on circulating blood exosomes. The study achieved an area under the curve of 0.73 when healthy donors were compared with patients with biopsy-positive breast cancer.

Cancer immunotherapy. Clinically relevant and actionable predictive biomarkers for cancer immunotherapy remain an area of huge unmet need. Since the arrival of anti–CTLA-4 and anti–PD-1/PD-L1 cancer immunotherapy and its clinical fruition with various U.S. Food and Drug Administration approvals granted for its use as standard-of-care cancer treatment in multiple cancer types, a few genomic and tissue biomarkers have been validated and approved for cancer immunotherapeutics. These include tumor PD-L1 expression levels (as companion diagnostics for pembrolizumab and as complementary diagnostics for nivolumab and atezolizumab)109,110 and, more recently, microsatellite instability status (with high microsatellite instability as a tumor type agnostic biomarker for pembrolizumab).111 Furthermore, strong evidence of tumor mutational load (or mutational burden) has been found to support its use as a predictive immuno-oncology biomarker.112-114 Nonetheless, alternative means of achieving immunotherapy biomarkers have been keenly sought in recent years, at least in part because of the practical issues surrounding invasive tumor tissue biopsies, potential sampling errors in needle biopsies especially in the setting of tumor heterogeneity, and limitations in attempting repeat tissue biopsies during therapies. Again, liquid biopsy represents one of the top priorities in the quest for optimal noninvasive immuno-oncology biomarkers.115

Again, ctDNA in liquid biopsy serves as a source for a more comprehensive representation of the tumor genomic status in immuno-oncology therapy and thus contributes as a potential substrate for immuno-oncology treatment biomarkers. Koeppel et al.116 reported a study in which tumor mutation load was assayed by cfDNA (i.e., ctDNA) using WES, rather than in tumor tissue DNA. They performed WES on cfDNA from 32 patients with different types of metastatic cancer in the MOSCATO 01 and/or MATCHR molecular triage trials (NCT01566019 and NCT02517892, respectively). WES mutation detection sensitivity was 92% in cfDNAs compared with targeted sequencing, whereas mutation detection sensitivity was 53% when cfDNA-WES was compared with tissue DNA-WES. For samples in which the presence of tumor DNA was confirmed in cfDNA, the tumor mutation load from the liquid biopsy was correlated with

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Beyond these nonvolatile metabolites, VOCs can now also be identified and measured in various headspace gas phases of human tissues, blood, and urine and even in exhaled breath. An emerging body of literature over the past decades has suggested that the feasibility and promise of VOC profiling or fingerprinting could be an attractive noninvasive cancer diagnostic in the future.\textsuperscript{125}

Pilot and proof-of-concept studies in the lung cancer field have increasingly been published in recent years using VOC profiling with gas chromatography/MS and various chemical sensor matrices including microfluidic chip sensors. Hence, the spectrum and concentrations of VOCs in breath samples can be captured with the sensors as correlates of the broad chemical constitution of the biospecimen without the absolute need for the identities of the specific VOC components. Cancer is now more regularly classified through the prism of the genomic lens with genomic alterations guiding precision therapeutics. This is particularly true as seen in genomic discoveries in recent years in lung adenocarcinoma. Peled et al\textsuperscript{126} previously reported a proof-of-concept in vitro pilot study using tumor cell VOC detection with nanomaterial-based sensors to profile genetic mutations of lung cancer cells (namely, \textit{EGFR} mutations, \textit{KRAS} mutations, and \textit{EML4-ALK} fusion). Breath analysis has also been adopted for the study of pulmonary nodules and for identification and characterization of lung cancer. Mazzone et al\textsuperscript{127} reported identification of exhaled breath VOC biosignatures of lung cancer using a colorimetric VOC sensor array in a study cohort of 229 participants (92 patients with lung cancer and 137 controls). The authors suggested optimizing the breath biosignature accuracy by incorporating clinical parameters (e.g., risk factors and histology). Peled et al\textsuperscript{128} reported the use of VOC profiling breath analysis to discriminate benign from malignant pulmonary nodules in a high-risk cohort of 19 patients with benign disease and 53 with malignant disease with similar smoking histories and comorbidities. More recently, Nardi-Agmon et al\textsuperscript{129} further reported the use of noninvasive breath biosignatures, as determined by gas chromatography/MS and a nanomaterial-based sensor array, to correlate with and monitor treatment response in advanced lung cancer in a small study of 39 patients and 143 collected breath samples. These applications could potentially have a notable impact on clinical decision making and therapeutics determination.

Various devices and technologies designed to detect VOCs for cancer diagnostics using not only exhaled breath but also other noninvasive body substrates such as urine are currently available. In addition to the more routine application of gas chromatography/MS used in electronic nose technology (eNose, Zutphen, Netherlands) with arrays of nonselective chemical sensors, other competing technologies are emerging such as the field asymmetric ion mobility spectrometry microchip.\textsuperscript{130} This microchip platform is a variant of ion mobility spectrometry,\textsuperscript{130} a method of distinguishing charged gaseous molecules according to differences in the speed at which they move through a buffer gas under the influence of an oscillating electric field. It is claimed to have
improved advantages in overcoming sample stability and sensitivity issues and in data analysis. VOC detection at low parts per billion (and in some cases, parts per trillion) levels is feasible in the field asymmetric ion mobility spectrometry microchip platform, enabling it to be well suited not only for clinical sample assaying but also for use as a potential future point-of-care measurement in a portable and convenient fashion. Another new exciting technology in development is the Nanobeak Sensor (Nanobeak Inc., New York, NY), which converges nanoelectronics, bioinformatics, and wireless technology to achieve a mobile point-of-care screening application based on chemical VOC sensing within a small Bluetooth device. The Nanobeak technology uses carbon nanotubes to detect VOCs with the invention originated from the National Aeronautics and Space Administration when it launched the nanosensor into orbit in 2007 to test and determine that it works well in outer space. Currently, a number of pilot clinical studies using these new breath biopsy technologies for cancer diagnostics are ongoing or are being planned (NCT02888366, NCT02781857, NCT02123030, NCT03275688, NCT01292369, NCT01386203, and NCT02612532).

CONCLUSION
In recent years, we have witnessed a revolutionary advancement in cancer medicine among the whole spectrum of cancer genomics, molecular genomics diagnostics, technological platform innovations, and cancer therapeutics. As a result, we have seen an unprecedented pace of progress in the expansion of cancer diagnostics on tumor tissues as well as beyond tissues in novel noninvasive molecular assays, in parallel with the ever-growing list of cancer therapeutics such as precision therapies and immunotherapeutic agents. Noninvasive molecular diagnostics beyond tissues have already found clinical utility and application particularly in the area of cfDNA/ctDNA genotyping/genomic profiling as a blood biopsy (liquid biopsy) technique. They have also been increasingly applied in longitudinal monitoring of therapy for early disease detection and in therapeutic response-resistance monitoring. Various other promising noninvasive cancer diagnostics assay platforms also include saliva biopsy, urine biopsy, stool biopsy, CSF biopsy, other forms of blood biopsy beyond cfDNA/ctDNA (e.g., proteomics and metabolomics), and even breath biopsy for VOC measurement. It is important to emphasize the crucial significance of committing appropriate resources and applying rigorous study designs for validating these promising assay platforms in large-scale prospective clinical studies to bring them to fruition. Moreover, rigorous scientific scrutiny of the various assay platforms remains indispensable to discern between hype and reality when assessing each novel molecular diagnostics platform that emerges.

References


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Liquid biopsy has been used extensively in solid malignancies to detect actionable driver mutations, to monitor treatment response, to detect recurrence, to identify resistance mechanisms, and to prognosticate outcome. Although many liquid biopsy sequencing platforms are being used, only five test kits have received government approval. We review representative literature on these government-approved liquid biopsy kits, which are primarily used to detect EGFR mutation in lung cancer and RAS (KRAS, NRAS, BRAF) mutations in colorectal carcinoma. Another emerging use of single-gene liquid biopsy is to detect PIK3CA mutations and to understand resistance to hormonal blockade in breast and prostate cancers. The two most commonly used next-generation sequencing (NGS) liquid biopsy tests (Guardant 360, Guardant Health; FoundationACT, Foundation Medicine Inc.) are discussed. The ability and the applicability of NGS platform to detect tumor mutation burden are also addressed. Finally, the use of circulating tumor DNA (ctDNA) to detect minimal residual disease may be the most important use of ctDNA in the setting of tumor heterogeneity. The ability to identify “shedders” and “nonshedders” of ctDNA may provide important insight into the clinicopathologic characteristics of the tumor and portend important prognostic significance regarding survival.

The use of liquid biopsy (primarily from blood) in solid malignancy provides a convenient and safe way to detect the presence of actionable driver mutations, to assess the resistance mechanisms to actionable driver mutations, to monitor treatment response, to detect early recurrence, to serve as an adjuvant to radiologic imaging as post-treatment surveillance, and to prognosticate the outcome of cancer treatment. Cell-free DNA, including ctDNA, circulating tumor cells, and exosomes containing tumor microRNAs can all be detected by liquid biopsy. The biologic nature of ctDNA, the various sequencing platforms used in liquid biopsy, and the various utilities of liquid biopsy have recently been expertly and comprehensively reviewed by Wan and colleagues. The many sequencing platforms used in liquid biopsy can be broadly summarized as nondigital, digital, and NGS. The performances of these individual platform have been reviewed extensively. However, only five liquid biopsy test kits are approved by government agencies.

DETECTION OF SPECIFIC ACTIONABLE GENOMIC ALTERATIONS BY LIQUID BIOPSY

Detection of Activating EGFR Mutations in Lung Cancer

Cobas EGFR mutations test version 2 (EGFR del19, L858R, T790M). The Cobas test (Roche Molecular Diagnostics, Pleasanton, CA) is the only U.S. Food and Drug Administration (FDA)–approved liquid biopsy to detect the two most common activating epidermal growth factor receptor (EGFR) mutations (EGFR del19 and EGFR L858R) for the selection of EGFR tyrosine kinase inhibitor. It was subsequently approved for the detection of the most common acquired resistance mutation, EGFR T790M, after progression with first- or second-generation EGFR tyrosine kinase inhibitors for selection of osimertinib to treat patients with EGFR T790M–positive non–small cell lung cancer (NSCLC; Table 1). ENSURE, a randomized phase III trial comparing erlotinib to platinum/gemcitabine chemotherapy as first-line treatment of EGFR-positive NSCLC provided the basis for the approval of detection of EGFR del19 and EGFR L858R. Additional large-scale real-life prospective trials (ASSESS, Europe and Japan; and IGNITE, Russia and China/South Korea/Taiwan) studying the feasibility and testing the concordance of using Cobas liquid biopsy versus tumor have been completed. In the IGNITE study, the concordance between 2,561 matched tissue/cytology and plasma samples was 80.5%, sensitivity was 46.9%, and specificity was 95.6%. In the ASSESS study, the concordance of mutation status in 1,162 matched samples was 89%, sensitivity was 46%, specificity was 97%, positive predictive value was 78%, and negative predictive value was 90%. Two combined single-arm phase II studies of osimertinib provided the basis for the approval for the detection of EGFR T790M. A European study (APPLE) investigating...
the use of liquid biopsy to detect EGFR T790M mutation is ongoing.\(^\text{19}\)

**Therascreen EGFR plasma RGQ PCR kit.** The Therascreen EGFR Plasma RGQ PCR test (Qiagen Inc., Venlo, the Netherlands) is approved in the European Union (E.U.; Conformité Européene-In Vitro Diagnostics) for detection of the two most common EGFR mutations (EGFR del19 and EGFR L858R) but not T790M (Table 1).\(^\text{20-23}\) The IFUM study provided the basis for adoption of this test in Europe.\(^\text{24,25}\)

**AmoyDx Super-ARMS EGFR mutation test kit.** The newest government-approved liquid biopsy, the AmoyDx Super-ARMS EGFR mutation test kit (AmoyDx, Xiamen, China), was approved on January 22, 2018, by the Chinese Food and Drug Administration to detect EGFR del19, EGFR L858R, and EGFR T790M mutations (Table 1).\(^\text{26-28}\) AURA17 is a single-arm study of osimertinib in China that provided the supporting evidence for the approval of this test kit.\(^\text{28}\)

**Role in diagnosis.** Although all three tests can detect the three “uncommon” EGFR mutations (L861Q, G719X, and S768I)—for which afatinib was approved for use in the United States on January 16, 2018—none of them is officially approved to detect them.\(^\text{29}\) Table 1 shows that across all three test kits, the sensitivity for detecting T790M seems to be lower than that for detecting two common activation mutations. The higher the prevalence of EGFR mutations (e.g., approximately 40%-50% in Asian populations), the lower the negative predictive value of the liquid biopsy (Table 1); this is based on the Cobas EGFR version 2 calculations. Thus, a negative EGFR plasma test result in a high-endemic region for EGFR mutations should be followed by a tumor tissue biopsy.

In addition, the National Institute of Health and Care Excellence in the United Kingdom recently published their technology summary of evidence of seven different liquid biopsy platforms.\(^\text{30}\) The four additional tests reviewed, in addition to the three government-approved tests, were the AmoyDx EGFR 29 mutation detection kit, AmoyDx Super-ARMS EGFR T790M mutation detection kit, Droplet Digital PCR (ddPCR) Dx system (Bio-Rad, Hercules, CA), and PANA Mutyper R EGFR kit (Panagene, Daejeon, Korea). The major summary finding is that plasma EGFR detection has specificity similar to but sensitivity lower than those of tumor biopsy. The resource impact to the health care system is similar to that for standard of care, but plasma testing could be cost-effective if this led to fewer tissue biopsies.\(^\text{30}\)

Going forward, increasing evidence suggests that the ability to identify detectable circulating EGFR mutations from liquid biopsy (“shedders” compared with “nonshedders”) has prognostic implications. In the FLAURA and AURA3 phase III trials (Table 2), although both shedders and nonshedders benefited from osimertinib, progression-free survival (PFS) in the osimertinib arm was numerically better for nonshedders than for shedders; this finding indicates that shedders in general have a higher tumor burden (Table 2).\(^\text{31}\) Additionally, among patients treated at National Taiwan University Hospital who progressed while receiving osimertinib, a retrospective genomic analysis that used plasma BEAMing technology (Sysmex Inostics, Hamburg, Germany) to detect EGFR mutations showed that, again, shedders had significantly shorter median PFS while receiving osimertinib, shorter PFS after progression on osimertinib, and shorter overall survival (OS) after osimertinib treatment (Table 2).\(^\text{32}\) Furthermore, 42.5% (17/40) of the shedders compared with only 7.7% (1/13) of nonshedders had brain metastases in this study, again indicating that shedders had more extensive/poor-prognosis disease than nonshedders. Finally, the “disappearance” of EGFR T790M at the time of progression during osimertinib treatment was associated with significantly shorter PFS after osimertinib therapy (Table 2), indicating more recalcitrant non–EGFR-mediated resistance mechanisms.\(^\text{32}\) Shedders of EGFR T790M usually have higher tumor burden with late-stage disease. Similarly, shorter PFS has been reported in shedders with EGFR L858R mutation than in nonshedders from a retrospective analysis of the EURTAC trial.\(^\text{33,34}\)

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**PRACTICAL APPLICATIONS**

- **Despite the widespread use of liquid biopsy in solid malignancy, only five distinct test kits have government approval: Cobas EGFR Mutations Test v2 (Roche Molecular Diagnostics; FDA approval for detection of EGFR del19, EGFR L858R, and EGFR T790M in lung cancer), Therascreen EGFR RGQ Plasma PCR kit (Qiagen Inc; E.U. approval for detection of EGFR del19 and EGFR L858R in lung cancer); AmoyDx Super-ARMS EGFR mutation test (AmoyDx; Chinese Food and Drug Administration approval for detection of EGFR del19, EGFR 858R, and EGFR T790M in lung cancer); OncoBEAM RAS CRC Kit (Sysmex Inostics; E.U. approval for detection of KRAS and NRAS mutations in colorectal cancer); and Idylla ctKRAS Mutation Test and Idylla ctNRAS-BRAF Mutation Test (Biocartis, Inc.; E.U. approval for detection of KRAS, NRAS, and BRAF mutations in colorectal cancer).**

- **Currently, liquid biopsy is most commonly used to detect actionable EGFR, RAS (KRAS, NRAS), and BRAF V600E mutations, with potentially in the future for detection of PIK3CA mutations.**

- **Liquid biopsy based on NGS can detect multiple genomic alterations (mutations, indel, amplification, rearrangement) in multiple actionable genes and also determine tumor mutation burden used to potentially select for immune checkpoint inhibitors. Eventually, liquid biopsy using NGS will supersede use of single/oligo gene liquid biopsy detection kits.**

- **Liquid biopsy to detect nonspecific ctDNA in tumors without clear driver mutations may be most useful in detecting minimal residual disease, which can account for tumor heterogeneity in the adjuvant setting.**

- **Distinguishing “shedders” and “nonshedders” of ctDNA may provide insight into tumor biology and prognostic significance.**
<table>
<thead>
<tr>
<th>PCR Kit</th>
<th>Therascreen EGFR Plasma RGQ PCR Kit</th>
<th>Cobas EGFR Mutation Test v2</th>
<th>AmoyDX Super-ARMS EGFR Mutation Detection Kit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approving Agency/Region</strong></td>
<td>European Union 98/79, Conformité Européene-In Vitro Diagnostics directive</td>
<td>U.S. FDA</td>
<td>Chinese FDA</td>
</tr>
<tr>
<td><strong>Date of Approval</strong></td>
<td>January 12, 2015</td>
<td>June 1, 2016 (EGFR del 19, EGFR L858R) September 28, 2016 (EGFR T790M)</td>
<td>January 22, 2018 (EGFR del 19, EGFR L858R, EGFR T790M)</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Qiagen</td>
<td>Roche</td>
<td>AmoyDx</td>
</tr>
<tr>
<td><strong>Sequencing Platform</strong></td>
<td>Scorpion Amplification Refractory MutaƟ on System</td>
<td>Scorpion Amplification Refractory MutaƟ on System</td>
<td>Scorpion Amplification Refractory Mutation system</td>
</tr>
<tr>
<td><strong>Detectable Technology</strong></td>
<td>Analog (real-time PCR)</td>
<td>Analog (real-time PCR)</td>
<td>Analog (real-time PCR)</td>
</tr>
<tr>
<td><strong>MAF Quantification</strong></td>
<td>SemiquanƟ taƟ ve</td>
<td>SemiquanƟ taƟ ve</td>
<td>SemiquanƟ taƟ ve</td>
</tr>
<tr>
<td><strong>No. of EGFR Mutations Detected</strong></td>
<td>29</td>
<td>42</td>
<td>41</td>
</tr>
<tr>
<td><strong>Major EGFR Mutations Detected</strong></td>
<td><em>EGFR del 19 (19 different mutations)</em>&lt;br&gt;<em>EGFR L858R</em>&lt;br&gt;<em>EGFR T790M</em>&lt;br&gt;<em>EGFR G719X (3 different mutations)</em>&lt;br&gt;<em>EGFR S761I</em>&lt;br&gt;<em>EGFR L861Q</em>&lt;br&gt;<em>EGFR exon 20 insertions (3 insertions)</em></td>
<td><em>EGFR del 19 (29 different mutations)</em>&lt;br&gt;<em>EGFR L858R (2 different mutations)</em>&lt;br&gt;<em>EGFR T790M</em>&lt;br&gt;<em>EGFR G719X (3 different mutations)</em>&lt;br&gt;<em>EGFR S761I</em>&lt;br&gt;<em>EGFR L861Q</em>&lt;br&gt;<em>EGFR exon 20 insertions (5 insertions)</em></td>
<td><em>EGFR del 19 (29 different mutations)</em>&lt;br&gt;<em>EGFR L858R</em>&lt;br&gt;<em>EGFR T790M</em>&lt;br&gt;<em>EGFR G719X (3 different mutations)</em>&lt;br&gt;<em>EGFR S761I</em>&lt;br&gt;<em>EGFR L861Q</em>&lt;br&gt;<em>EGFR exon 20 insertions (5 insertions)</em></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td><em>EGFR del 19, EGFR L858R, EGFR Del 19 and EGFR L858R</em></td>
<td><em>EGFR del 19, EGFR L858R, EGFR T790M</em></td>
<td><em>EGFR del 19, EGFR L858R, EGFR T790M</em></td>
</tr>
<tr>
<td><strong>Study(ies) Supporting Approval</strong></td>
<td>IFUM ENSURE (YO25121)</td>
<td>ENSURE (YO25121)</td>
<td>Single-center, single-arm study (First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, China)</td>
</tr>
<tr>
<td><strong>Comparator Tissue Test</strong></td>
<td>Therascreen EGFR test (tissue use)</td>
<td>Cobas EGFR mutation test v2 (tissue test) NGS on an Illumina MiSeq</td>
<td>AmoyDx EGFR 29 mutation detection kit (tissue)</td>
</tr>
<tr>
<td><strong>No. of Patients</strong></td>
<td>859 with tumors successfully screened 652 with successfully paired tumor/plasma analyzed</td>
<td>601 with tumors successfully screened 431 with successfully paired tumor/plasma analyzed and validated 217 enrolled</td>
<td>109 screened 61 with tissue positive for all EGFR mutations 50 with plasma positive for all EGFR mutations</td>
</tr>
</tbody>
</table>

Continued
### TABLE 1. Approved Liquid Biopsy Test Kits for Detection of Activating and Resistance Mutations in Non–Small Cell Lung Cancer (Cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Therascreen EGFR Plasma RGQ PCR Kit</th>
<th>Cobas EGFR Mutation Test v2</th>
<th>AmoyDX Super-ARMS EGFR Mutation Detection Kit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Data</strong></td>
<td>Screening for all patients:</td>
<td>Screening for all patients</td>
<td>Of 61 patients positive for EGFR mutations from tumor, 50 were also detected by plasma</td>
</tr>
<tr>
<td></td>
<td>Of 105 patients positive for EGFR mutations from tumor, 69 (65.7%) were detected by plasma</td>
<td>Of 210 patients positive for EGFR mutations from tumor, 161 (76.7%) were detected by plasma</td>
<td>Of 48 patients negative for EGFR mutations from tumor, 48 were also negative for EGFR mutations by plasma</td>
</tr>
<tr>
<td></td>
<td>Of 547 patients negative for EGFR mutations from tumor, 546 (99.8%) were negative for EGFR mutation by plasma</td>
<td>Of 221 patients negative for EGFR mutations from tumor, 217 (98.2%) were negative for EGFR mutation by plasma</td>
<td></td>
</tr>
<tr>
<td><strong>Performance Characteristics</strong></td>
<td>Sensitivity: 65.7% (95% CI, 55.8%–74.7%)</td>
<td>Prevalence: 15%</td>
<td>Sensitivity: 82% (95% CI, 72.3%–91.6%)</td>
</tr>
<tr>
<td></td>
<td>Specificity: 99.8% (95% CI, 99%–100%)</td>
<td>PPV: 88.6% (95% CI, 79.7%–96.6%)</td>
<td>Specificity: 100%</td>
</tr>
<tr>
<td></td>
<td>Concordance: 94.3% (95% CI, 92.3%–96.0%)</td>
<td>PPV: 96.0% (95% CI, 94.3%–97.6%)</td>
<td>PPV: 81.4% (95% CI, 71.4%–91.3%)</td>
</tr>
<tr>
<td></td>
<td>PPV: 98.6% (95% CI, 92.3%–100%)</td>
<td>Prevalence: 40%</td>
<td>NPV: 100%</td>
</tr>
<tr>
<td></td>
<td>NPV: 93.8% (95% CI, 91.5%–95.6%)</td>
<td>Prevalence: 80%</td>
<td>Concordance: 89.9% (95% CI, 84.3%–95.6%)</td>
</tr>
<tr>
<td><strong>Clinical Outcome Data</strong></td>
<td>ORR (EGFR del 19 + L858R)</td>
<td>PFS benefit of erlotinib over chemotherapy (ITT population, n = 217)</td>
<td>ORR (All patients: 64.3% (95% CI, 48%–78%; n = 42)</td>
</tr>
<tr>
<td></td>
<td>Tumor+/plasma+: 72.2% (95% CI, 61.0%–81.6%); tumor+/plasma−: 63.6% (95% CI, 46.6%–77.8%)</td>
<td>HR, 0.33 (95% CI, 0.23–0.47); log-rank test p &lt; .0001</td>
<td>Tumor+/plasma+: 65.7% (95% CI, 48%–81%; n = 35)</td>
</tr>
<tr>
<td></td>
<td>ORR (EGFR del 19)</td>
<td>PFS benefit of erlotinib over chemotherapy (tumor+/plasma−; n = 137)</td>
<td>Tumor+/plasma−: 57.15% (95% CI, 18%–90%)</td>
</tr>
<tr>
<td></td>
<td>Tumor+/plasma+: 82.2% (95% CI, 68.7%–90.7%); tumor+/plasma−: 65.0% (95% CI, 43.5%–73.7%)</td>
<td>HR, 0.29 (95% CI, 0.19–0.45); log-rank test p &lt; .0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ORR (EGFR L858R)</td>
<td>PFS benefit of erlotinib over chemotherapy (tumor+/plasma−; n = 42)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Median PFS (all enrolled patients)</td>
<td>HR, 0.37 (95% CI, 0.50–0.90)</td>
<td></td>
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<tr>
<td></td>
<td>All enrolled patients: 9.7 mo (95% CI, 8.5–11.0 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor+/plasma+: 10.2 mo (95% CI, 8.5–12.5 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EGR del 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>All: 9.6 mo (95% CI, 8.0–11.0 mo)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tumor+/plasma+: 10.3 mo (95% CI, 8.5–12.4 mo)</td>
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</tbody>
</table>

**T790M**

**continued**
<table>
<thead>
<tr>
<th>Validation Study</th>
<th>Primary Data</th>
<th>Comparator Tissue Test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Therascreen EGFR Plasma RGQ PCR Kit</strong></td>
<td><strong>551 of 710 (78%) patients enrolled in both trials had paired tissue and plasma samples</strong>&lt;br&gt;<strong>416 of 551 (75.5%) patients were plasma positive for T790M, 127 (23.0%) were plasma negative for T790M, and 8 patients had invalid plasma tests</strong></td>
<td><strong>240 patients</strong></td>
</tr>
<tr>
<td><strong>Cobas EGFR Mutation Test v2</strong></td>
<td></td>
<td><strong>Cobas EGFR mutation test v2 (tissue test)</strong></td>
</tr>
<tr>
<td><strong>AmoyDX Super-ARMS EGFR Mutation Detection Kit</strong></td>
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</tr>
</tbody>
</table>

**Performance Parameters**

<table>
<thead>
<tr>
<th><strong>EGFR T790M</strong></th>
<th><strong>EGFR del19</strong></th>
<th><strong>EGFR L858R</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity: 61% (95% CI, 57%–66%)&lt;br&gt;Specificity: 79% (95% CI, 70%–85%)&lt;br&gt;Concordance: 65% (95% CI: 61%–69%)</td>
<td>Sensitivity: 85% (95% CI, 81%–89%)&lt;br&gt;Specificity: 98% (95% CI, 95%–100%)&lt;br&gt;Concordance: 90% (95% CI, 87%–92%)</td>
<td>Sensitivity: 76% (95% CI, 69%–82%)&lt;br&gt;Specificity: 98% (95% CI, 96%–99%)&lt;br&gt;Concordance: 91% (95% CI, 88%–93%)</td>
</tr>
</tbody>
</table>

**Clinical Outcome**

<table>
<thead>
<tr>
<th><strong>ORR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>T790M tumor+/plasma+ : 64% (95% CI, 57%–70%; n = 235)&lt;br&gt;T790M tumor+/plasma- : 70% (95% CI, 62%–77%; n = 155)</td>
</tr>
</tbody>
</table>

**References**

20-25, 11-13, 18, 23, 26-28

*Analog detection (also known as real-time PCR) uses fluorescent markers that attach to specific mutation sites, making them detectable; fluorescence in the sample is detected as a whole. In digital PCR, the sample is separated into many partitions, each tested individually, providing a lower threshold of detection.*

**Can detect the level of ctDNA at or above threshold limit, fully quantitative can measure the level of ctDNA in a sample.**

**Abbreviations:** FDA, U.S. Food and Drug Administration; PCR, polymerase chain reaction; MAF, mutant allele frequency; iFUM, Iressa Follow up Measure Study; NGS, next-generation sequencing; ORR, overall response rate; NPV, negative predictive value; PPV, positive predictive value; ITT, intention-to-treat; HR, hazard ratio; PFS, progression-free survival; NA, not applicable.
TABLE 2. Survival Outcome (Progression-Free Survival, Overall Survival, and Survival After Osimertinib Progression) of EGFR T790M Shedders Versus Nonsedders

<table>
<thead>
<tr>
<th>EGFR Variable</th>
<th>Osimertinib</th>
<th>Gefitinib/Erlotinib</th>
<th>HR (95% CI); p Value</th>
<th>Overall (n = 556)</th>
<th>Shedders (n = 359)</th>
<th>Nonsedders (n = 124)</th>
<th>HR (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>279</td>
<td>277</td>
<td></td>
<td>183</td>
<td>176</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>18.9 (15.2–21.4) mo</td>
<td>10.2 (9.6–11.1) mo</td>
<td>0.46 (0.37–0.57); p &lt; .0001</td>
<td>15.2 (13.7–20.7) mo</td>
<td>9.7 (8.4–11.1) mo</td>
<td>0.44 (0.34–0.57); p &lt; .0001</td>
<td>23.5 (17.8–24.3) mo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EGFR Variable</th>
<th>Osimertinib</th>
<th>Gefitinib/Erlotinib</th>
<th>HR (95% CI); p Value</th>
<th>Overall (n = 419)</th>
<th>Shedders (n = 272)</th>
<th>Nonsedders</th>
<th>HR (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>279</td>
<td>140</td>
<td></td>
<td>116</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>10.1 (8.3–12.3) mo</td>
<td>4.4 (4.2–5.6) mo</td>
<td>0.30 (0.23–0.41); p &lt; 0.0001</td>
<td>8.2 (6.8–97) mo</td>
<td>4.2 (41.5–1.1) mo</td>
<td>0.42 (0.29–0.61) NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EGFR Variable</th>
<th>Osimertinib</th>
<th>Chemotherapy</th>
<th>HR (95% CI); p Value</th>
<th>Overall (n = 419)</th>
<th>Shedders (n = 272)</th>
<th>Nonsedders</th>
<th>HR (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>38</td>
<td>9</td>
<td></td>
<td>21</td>
<td>8</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Median PFS (during osimertinib treatment)</td>
<td>5.0 (3.8–9.0) mo</td>
<td>14.5 (7.2–NR) mo</td>
<td>0.008</td>
<td>7.7 (5.0–NR) mo</td>
<td>17.8 (12.2–NR) mo</td>
<td>0.031</td>
<td>5.0 (3.0–NA) mo</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; PFS, progression-free survival; NR, not reached; NA, not available; OS, overall survival.
Detection of *RAS* and *BRAF* Mutations in Colorectal Cancer

Retrospective analysis of two randomized phase III trials in metastatic colorectal cancer (mCRC; PRIME, CRYSTAL) comparing the addition of anti-EGFR antibody to chemotherapy versus chemotherapy alone indicated that multiple *KRAS*, *NRAS*, and *BRAF* mutations modulate the clinical response to anti-EGFR antibodies. In particular, an additional 14.7% (CRYSTAL) to 17% (PRIME) of non–exon 2 *KRAS* mutations were detected, which also did not benefit from EGFR monoclonal treatment, hence the detection of *KRAS* mutation should be extended to non–exon 2 *KRAS* mutations. The E.U. has approved three sets of liquid biopsy kits from two different companies that detect an extended spectrum of *RAS* mutations to select patients with mCRC who will potentially benefit from anti-EGFR therapy and avoid the unnecessary expense and additional side effects of anti-EGFR antibody treatment.

**OncoBEAM RAS CRC kit (*KRAS* and *NRAS*).** Several studies using different tissue comparator tests provided the evidence for approval of OncoBEAM RAS detection kit (Sysmex Inostics; Table 3) for the detection of *KRAS* and *NRAS* mutations in mCRC. Not surprisingly, when a much more sensitive tissue comparator test, such as NGS, is used, the sensitivity and specificity of BEAMing technology are not as high (e.g., with the Sanger sequencing method as the comparator; Table 3). The additional use of BEAMing to detect *KRAS* mutations includes real-time monitoring of treatment, detection of resistance mechanisms, and early detection of relapse and/or residual disease; these have been concisely reviewed by an expert task force panel.

**Idylla ctKRAS mutation test and Idylla ctNRAS-BRAF mutation test.** The RASANC study provided the supporting evidence for the approval of the Idylla tests (Biocartis, Inc., Jersey City, NJ) for the detection of *KRAS*, *NRAS*, and *BRAF* in mCRC. Primary tumor removal, metachronous status, absence of liver metastases, and peritoneal carcinomatosis were significantly associated with mutant *RAS* tumor and negative plasma status, indicating the difference between shedders and nonshedders.

In head and neck cancer, additional use of liquid biopsy to detect *RAS* mutations has been reported to identify resistance to cetuximab (anti-EGFR antibody)-based therapy. However, the resistance to anti-EGFR antibody therapy is not limited to *RAS* mutations based on liquid biopsy.

**BRAF V600E**

*BRAF* V600E mutation is a validated and actionable driver mutation in melanoma and NSCLC. Surprisingly, to date there is little published literature on the clinical use of liquid biopsy to detect *BRAF* V600E mutation in melanoma and NSCLC. Most of the literature on liquid biopsy for *BRAF* V600E is in mCRC, especially when used in extended-spectrum *RAS* mutational analysis to select patients for anti-EGFR treatment (Table 3). Not surprisingly, a greater amount of *BRAF* V600E detected at liquid biopsy was associated with worse prognosis for survival in mCRC (hazard ratio [HR], 7.33; 95% CI, 1.04–2.89; *p* = .002) in a multivariate analysis that included age, tumor location, carcinoembryonic antigen (CEA), *KRAS* mutational status, and amount of circulating cell-free DNA.

**PIK3CA Mutations**

Although no approved drug specifically targets *PIK3CA* mutations, and *PIK3CA* mutations have not been conclusively shown to be a driver mutation, *PIK3CA* mutations may confer sensitivity to *PIK3CA* inhibitors. Two randomized phase III trials have investigated the potential clinical benefit of the addition of buparlisib (BKM210), a class 1 pan-*PIK3CA* inhibitor, to fulvestrant in hormone receptor–positive, HER2-negative patients whose disease is refractory to aromatase inhibitors (AIs; BELLE-2) and additionally refractory to mTOR inhibition (BELLE-3). Both trials investigated the presence of *PIK3CA* mutations, established by using BEAMing technology, and its implication for clinical outcome. Overall, the most common *PIK3CA* mutations identified from ctDNA from BELLE-3 were H1047R (39.7%), E545K (36.8%), E542K (18.4%), and H1047L (5.1%).

The sensitivity of the plasma *PIK3CA* mutations compared with tissue *PIK3CA* mutations in BELLE-2 was 71.2% (99/139), specificity was 79.2% (244/307), and overall concordance was 76.7% (342/446). Similarly, for BELLE-3, sensitivity was 80% (70/87), specificity was 87% (142/163), and concordance was 84.8% (212/250). The lower concordance in BELLE-2 probably results from the fact that detection of *PIK3CA* mutation in tumor is performed by using Sanger sequencing, which is not as sensitive as BEAMing technology. The presence of *PIK3CA* mutations in plasma corresponded to improved PFS in patients who received buparlisib in addition to fulvestrant compared with patients who received only fulvestrant in both BELLE-2 and BELLE-3 trials (Table 4). However, neither trial analyzed the prognostic significance of shedders versus nonshedders of *PIK3CA* mutations.

The role of *PIK3CA* mutation in breast cancer is being further evaluated in two phase III trials: SOLAR-1 (NCT02437318) is comparing alpelisib (a PI3KA inhibitor) and fulvestrant versus fulvestrant alone, with a prospective analysis of *PIK3CA* mutations in ctDNA, and SANDPIPER (NCT02340221) is comparing taselisib (GDC-0032) and fulvestrant versus fulvestrant alone in *PIK3CA*-mutant breast cancer as determined by Cobas testing. Otherwise, the eligibility criteria for both trials are similar to those of BELLE-2 (disease that is refractory to AI). If these trials will lead to the eventual approval of *PIK3CA* inhibitors, then *PIK3CA* mutations detection will become very important.

The prognostic significance of pretreatment plasma *PIK3CA* in cervical cancer was also investigated in 117 patients with cervical cancer treated in Hong Kong over a period of 10 years (1997 to 2007). ddPCR was used to detect *PIK3CA* E542K and E545K mutations. Overall, 26 of 117 (22.2%) patients were identified (23.7% in squamous cell carcinoma of...
<table>
<thead>
<tr>
<th>Table 3. Performance Characteristics of OncoBEAM RAS CRC Kit, Idylla ctKRAS, and Idylla ctNRAS-BRAF Mutation Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CE Mark Approval Date</strong></td>
</tr>
<tr>
<td><strong>Technology</strong></td>
</tr>
<tr>
<td><strong>Amount of Plasma Needed, mL</strong></td>
</tr>
<tr>
<td><strong>Hands-on Time, min</strong></td>
</tr>
<tr>
<td><strong>Turnaround Time</strong></td>
</tr>
</tbody>
</table>
| **Gene Coverage**  | 34 mutations: 16 KRAS and 18 NRAS  
Exon 2: codons 12 and 13  
Exon 3: codons 59 and 61  
Exon 4: codons 117 and 146 | 21 KRAS  
Exon 2: codons 12 and 13  
Exon 3: codons 59 and 61  
Exon 4: codons 117 and 146 | 18 NRAS  
Exon 2: codons 12 and 13  
Exon 3: codons 59 and 61  
Exon 4: codons 117 and 146  
5 BRAF | Exon 15: codon 600 |
| **Sensitivity in Plasma, %**  | 0.02–0.04 | 0.5 | 0.5 |
| **MAF Quantification**  | Quantitative | Semiquantitative | Semiquantitative |
| **Clinical Validity Measures**  | OncoBEAM RAS CRC Kit, Instructions for Use OBMRASIVD7  
Tissue comparator test: standard of care tissue testing  
Sensitivity: 92.6% (112/121)  
Specificity: 94.0% (110/117)  
Concordance: 93.3% (222/238)  
Grasselli et al, 2017 (n = 146)38  
Tissue comparator test: PCR  
Sensitivity: 89%  
Specificity: 90%  
Concordance: 89.7%  
PPV: 84%  
NPV: 93% | RASANC study (n = 198)45,46  
Comparator test: plasma-based NGS analysis with sensitivity of 0.2%  
KRAS+ (n = 84)  
NRAS+ (n = 6)  
BRAF+ (n = 13) | RAS: Sensitivity: 97.8% (90/92)  
RAS: Specificity: 95.3% (101/106)  
RAS: Concordance: 96.5% (191/198)  
KRAS: Concordance: 96%  
NRAS: Concordance: 100%  
BRAF: Concordance: 99.5% |
| **Clinical Outcome**  | Grasselli et al, 2017 (n = 146)38  
Median OS:  
Tissue KRAS-wild-type: 39.1 mo  
Tissue KRAS-mutated: 28.7 mo  
Plasma KRAS-wild-type: 42.9 mo  
Plasma KRAS mutated: 27.8 mo | NR |

Abbreviations: CE, Conformité Européene; PCR, polymerase chain reaction; MAF, mutant allele frequency; PPV, positive predictive value; NPV, negative predictive value; NGS, next-generation sequencing; NR, not reported.
### TABLE 4. Clinical Outcomes of BELLE-2 and BELLE-3 According to PKI3CA Mutation Status in Tumor and Plasma

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Population</th>
<th>ctDNA PKI3CA+</th>
<th>ctDNA PKI3CA−</th>
<th>Tumor PKI3CA+</th>
<th>Tumor PKI3CA−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BELLE-2*</td>
<td>576</td>
<td>571</td>
<td>87</td>
<td>113</td>
<td>199</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>11.8 (9.3–14.7)</td>
<td>7.7% (5.7–10.2)</td>
<td>18.4 (10.9–28.1)</td>
<td>3.5 (1.0–8.8)</td>
<td>11.6 (7.5–16.8)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>6.9 (6.8–7.8)</td>
<td>5.0 (4.0–5.2)</td>
<td>7.0 (5.0–10.0)</td>
<td>3.2 (2.0–5.1)</td>
<td>6.8 (4.7–8.5)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.78 (0.67–0.89)</td>
<td>0.58 (0.41–0.82)</td>
<td>1.02 (0.79–1.30)</td>
<td>1.18 (0.4 9–2.85)</td>
<td>0.98 (0.72–1.32)</td>
</tr>
<tr>
<td>p Value</td>
<td>.00021 (1-sided)</td>
<td>.001 (1-sided)</td>
<td>.557 (1-sided)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>BELLE-3**</td>
<td>289</td>
<td>143</td>
<td>100</td>
<td>35</td>
<td>132</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>3.9 (2.8–4.2)</td>
<td>1.8 (1.5–2.8)</td>
<td>4.2 (2.8–6.7)</td>
<td>1.6 (1.4–2.8)</td>
<td>3.9 (2.8–4.3)</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>0.67 (0.53–0.84)</td>
<td>0.46 (0.29–0.73)</td>
<td>0.73 (0.53–1.00)</td>
<td>0.39 (0.23–0.65)</td>
<td>0.81 (0.59–1.12)</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>.0030</td>
<td>.0031</td>
<td>.026</td>
<td>&lt; .0001</td>
<td>.099</td>
</tr>
</tbody>
</table>

*BELLE-2: Women who were estrogen receptor–positive or progesterone receptor–positive, human epidermal growth factor receptor 2–negative, aromatase inhibitor refractory. ctDNA PKI3CA determined by BEAMing polymerase chain reaction; tumor PKI3CA determined by Sanger sequencing.

**BELLE-3: Women who were estrogen receptor-positive or progesterone receptor–positive, human epidermal growth factor receptor 2–negative, aromatase inhibitor refractory, and refractory to mTOR inhibition. ctDNA PKI3CA determined by Inostics BEAMing polymerase chain reaction, covering exons 9 and 20; tumor PKI3CA determined by Cobas PIK3CA assay covering exons 7, 9, and 20.

Abbreviations: ORR, overall response rate; NR, not reported; NE, not evaluable; PFS, progression-free survival; HR, hazard ratio.
the cervix and 15.0% in adenocarcinoma of the cervix). The presence of plasma PIK3CA mutations was associated with high pathologic grade and large tumor size (mean tumor size, 4 cm) compared with 3 cm for patients negative for plasma PIK3CA mutations but was not associated with age, clinical stage, presence or absence of lymphovascular invasion, or pelvic lymph node metastasis. Although PIK3CA mutation was associated with shortened disease-free survival and OS on univariate analysis, on multivariate analysis PIK3CA mutation did not affect disease-free survival (HR 1.449; p = .464) or OS (HR 1.261; p = .643). Going forward, in analyses of larger cohorts of patients with cervical cancer who have uniform stage, histology, histologic grade, and treatment modality and are from a more contemporaneous treatment period, plasma PIK3CA mutations may turn out to be an important prognostic factor in cervical cancer. Liquid biopsy for PIK3CA mutation has also been investigated in small numbers of patients with bladder cancer and mCRC.58,59

**HER2 Amplification**

HER2 amplification was validated as an actionable target in breast cancer in 2001 and in gastric adenocarcinoma in 2010.60,61 The gold standard of detecting HER2 amplification in breast cancer is by immunohistochemistry or florescence in situ hybridization. Given the generally ready availability of tumor tissue from patients with breast cancer, there is scant literature on the use of liquid biopsy to detect or to monitor HER2 amplification at diagnosis or during treatment, respectively. Small studies have demonstrated that HER2 amplification detected in plasma correlates well with tumor HER2 amplification and that the level of HER2 amplification can be used to monitor treatment and recurrence in gastric cancer.62,63 HER2 amplification was successfully identified by using a liquid biopsy NGS panel to identify driver mutations to enroll in a basket targeted therapy trial that included HER2 inhibition.64

### Table 5. Effect of ESR1 Mutations on Clinical Outcome in Patients Receiving Endocrine Therapies in SoFEA Trial

<table>
<thead>
<tr>
<th>Variable</th>
<th>Exemestane</th>
<th>Fulvestrant Regimens</th>
<th>Hazard Ratio (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ESR1 Wild-Type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients (n)</td>
<td>39</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.0 (3.0–11.5)</td>
<td>5.7 (3.0–8.5)</td>
<td></td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>22.8 (17.6–32.4)</td>
<td>12.8 (5.7–27.0)</td>
<td></td>
</tr>
<tr>
<td><strong>ESR1-Mutated</strong></td>
<td></td>
<td>Exemestane</td>
<td></td>
</tr>
<tr>
<td>Patients (n)</td>
<td>18</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>2.6 (2.4–6.2)</td>
<td>2.6 (2.4–6.2)</td>
<td>0.52 (CI, 0.30–0.92); .02</td>
</tr>
<tr>
<td>Median OS, mo (95% CI)</td>
<td>12.8 (5.7–27.0)</td>
<td>12.8 (5.7–27.0)</td>
<td>1.65 (0.81–3.38); .16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR1 Wild-Type</th>
<th>Fulvestrant Regimens</th>
<th>Exemestane</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>59</td>
<td>39</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>8.0 (3.0–11.5)</td>
<td>5.4 (3.7–81)</td>
</tr>
</tbody>
</table>

**USE OF LIQUID BIOPSY TO IDENTIFY ACTIONABLE GENOMIC ALTERATIONS**

**HER2 Inhibition**

HER2 inhibition can be used to monitor treatment and recurrence in gastric HER2 inhibition.64 To enroll in a basket targeted therapy trial that included using a liquid biopsy NGS panel to identify driver mutations respectively. Small studies have demonstrated that HER2 amplification detected in plasma correlates well with tumor amplification and that the level of HER2 amplification was validated as an actionable target in breast cancer in 2001 and in gastric adenocarcinoma in 2010.60,61 The gold standard of detecting HER2 amplification in breast cancer is by immunohistochemistry or florescence in situ hybridization. Given the generally ready availability of tumor tissue from patients with breast cancer, there is scant literature on the use of liquid biopsy to detect or to monitor HER2 amplification at diagnosis or during treatment, respectively. Small studies have demonstrated that HER2 amplification detected in plasma correlates well with tumor HER2 amplification and that the level of HER2 amplification can be used to monitor treatment and recurrence in gastric cancer.62,63 HER2 amplification was successfully identified by using a liquid biopsy NGS panel to identify driver mutations to enroll in a basket targeted therapy trial that included HER2 inhibition.64

Detection of ESR1 mutation (primarily in the ligand-binding domain) in plasma has been investigated as a resistance mechanism to an AI in two randomized phase III trials, SoFEA (Study of Faslodex Versus Exemestane With or Without Arimidex) and PALOMA3 (Palbociclib Combined With Fulvestrant in Hormone Receptor–Positive HER2-Negative Metastatic Breast Cancer After Endocrine Failure), using the Bio-Rad QX-200 ddPCR system. In the SoFEA analysis, patients with mutant ESR1 in the exemestane treatment arm had significantly worse PFS (p = .01) than those without mutated ESR1. Similarly, PFS was significantly improved (p = .02) in patients with mutant ESR1 when they received fulvestrant-containing regimens but not (p = .77) in patients with wild-type ESR1 (Table 5). On the other hand, not surprisingly, the retrospective analysis of the PALOMA3 showed that both ESR1-mutated (HR 0.43; 95% CI, 0.25–0.74; p = .002) and ESR1 wild-type (HR 0.49; 95% CI, 0.35–0.70; p < .001) patients benefited from the addition of palbociclib to fulvestrant compared with those receiving placebo and fulvestrant because palbociclib is a CDK4/6 inhibitor (Table 6).65

Together, these two trials suggest that for patients who progressed while receiving a nonsteroidal AI and have detectable ESR1 mutations, it is best to switch to fulvestrant-containing regimens, such as fulvestrant and palbociclib. For patients who progressed while receiving a nonsteroidal AI and have no detectable ESR1 mutations, switching to an irreversible AI, such as exemestane, remains a treatment option before proceeding to fulvestrant-containing regimens. These are hypothesis-generating observations because only 161 of 723 (22.3%) patients enrolled in the SoFEA and only 360 of 551 (65.3%) patients

![asco.org/edbook | 2018 ASCO EDUCATIONAL BOOK 987](image-url)
enrolled in PALOMA3 had plasma available and successfully analyzed.

In the PALOMA3 trial, logistic multivariate analysis showed that the presence of plasma ESR1 mutations was negatively associated with tamoxifen treatment only (odds ratio [OR], 0.06; 95% CI, 0.01–0.45; p = .01) and positively associated with sensitivity to endocrine therapy (OR, 3.95; 95% CI, 1.54–6.39; p = .002), and visceral metastasis (OR, 1.74; 95% CI, 1.02–2.98; p = .04). Importantly, multivariate analysis of the PFS benefit in PALOMA3 showed a negative association with plasma ESR1-mutated genotype (HR 1.4; 95% CI, 1.07–2.08; p = .02), even after factoring in the significant benefit from palbociclib.65

Recent analysis of a large trial of first-line AI therapy in breast cancer indicated that ESR1 mutations may play a role in AI resistance, but other resistance mechanisms, such as KRAS, have been identified.66 Finally, liquid biopsy using NGS indicated multiple resistance mechanisms to AI in addition to ESR1 mutations.67

**Androgen Receptor Variant 7**

A splice variant of the androgen receptor variant 7 (AR-V7) that deletes the ligand domain of AR isolated from circulating tumor cells in the plasma is involved in de novo and acquired resistance to abiraterone (an androgen synthesis inhibitor) and enzalutamide (an AR ligand–binding domain antagonist), both of which have been approved for the treatment of castration-resistant prostate cancer (Table 7). In multivariable Cox regression analysis stratified by treatment type, AR-V7 detection remained independently predictive of prostate-specific antigen–defined PFS (HR 8.2; 95% CI, 2.7–24.9; p < .001), clinical/radiographic PFS (HR 4.9; 95% CI, 1.7–13.8; p = .003), or OS (HR 5.0; 95% CI, 1.3–19.8; p = .021; Table 7).68 Further study has indicated that AR amplification was associated with resistance to enzalutamide, and mutations (H874Y, T877A, D879E, L881I, E893K, and M895V) in the ligand-binding domain of AR are more associated with resistance to abiraterone.69 More recently, a longitudinal multiplex targeting sequencing of plasma from a study of 65 patients with castration-resistant prostate cancer receiving enzalutamide indicated that besides AR amplification of AR mutations, RB1 loss (p = .01) and MET copy number gain/amplification (p = .2) were significantly associated with shorter PFS after adjustment for the presence of ctDNA.70 Overall mutations in the direct target of hormonal blockade can partially explain the resistance to hormonal treatment of breast and prostate cancer. However, the advent of NGS liquid biopsy has allowed the discovery a much more complex pattern of resistance mechanisms.

**NEXT-GENERATION SEQUENCING PLATFORMS**

Liquid biopsy using NGS will be the dominant platform, with its increased depth of coverage, simultaneous multigene sequencing, and ability to simultaneously detect all modes of genomic alterations (point mutations, insertion/deletion [indel], amplification, and gene rearrangements) to account for both tumor heterogeneity and multiple resistance mechanisms and determination of tumor mutation burden (TMB). The two most common commercially used liquid biopsies are Guardant360 (Guardant Health, Redwood City, CA) and FoundationACT (Foundation Medicine Inc., Cambridge, MA). As listed in Table 8, the limit of detection and

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**Table 6. Effect of ESR1 Mutations on Clinical Outcome in Patients Receiving Endocrine Therapies in PALOMA3 Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESR1-Mutated</th>
<th>ESR1 Wild Type</th>
<th>Odds Ratio or Hazard Ratio (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>Palbociclib + Fulvestrant</td>
<td>Placebo + Fulvestrant</td>
<td>Statistical Consideration</td>
</tr>
<tr>
<td>ORR, %</td>
<td>17.5</td>
<td>3.6</td>
<td>5.94* (0.78–270.5); .06</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>9.4 (5.3–11.1)</td>
<td>3.6 (2.0–5.5)</td>
<td>0.43** (0.25–0.74); .002</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR1 Wild Type</th>
<th>Palbociclib + Fulvestrant</th>
<th>Placebo + Fulvestrant</th>
<th>Statistical Consideration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>177</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>21.5</td>
<td>14.1</td>
<td>1.66* (0.81–3.61); .14</td>
</tr>
<tr>
<td>Median PFS, mo (95% CI)</td>
<td>9.5 (9.2–NE)</td>
<td>5.4 (3.5–7.4)</td>
<td>0.49** (0.35–0.70); ≤ .001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ESR1 Status Available</th>
<th>ESR1 Wild Type</th>
<th>ESR1-Mutated</th>
<th>Odds Ratio or Hazard Ratio (95% CI); p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>261</td>
<td>91</td>
<td></td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>9.2 (7.4–10.9)</td>
<td>7.3 (3.7–9.1)</td>
<td>1.46** (1.06–2.02); .02</td>
</tr>
</tbody>
</table>

*Odds ratio (univariate analysis).
**Hazard ratio (univariate analysis).
Abbreviations: ORR, overall response rate; NE, not evaluable.
the gene panel of Guardant360 has evolved over time. It is important to be aware of the number of exact genes included in the NGS sequencing platform by consulting with the company websites because technology advances will lead to increased complexities of the NGS panel being offered commercially. It is also important to note how the interpretation of the literature depends on the various versions of Guardant360.

Among the many other NGS liquid biopsy platforms that are available or under development are Oncomine Lung cfDNA Assay (ThermoFisher Scientific, Waltham, MA),\(^8\) Archer Reveal ctDNA (ArcherDX, Boulder, CO),\(^8\) Onco-type SEQ (Genomic Health, Redwood City, CA),\(^9\) LiquidDx (MolecularMD, Portland, OR),\(^10\) CancerIntercept Detect and CancerIntercept Monitor (Pathway Genomics, San Diego, CA),\(^11\) OptiSeq NGS Pan-Cancer Panel (DiCarta, Richmond, CA),\(^12\) and PlasmaSELECT (Personal Genome Diagnostics, Baltimore, MD).\(^13\)

### USE OF LIQUID BIOPSY TO DETERMINE TUMOR MUTATION BURDEN

TMB is usually expressed as number of mutations per megabase of DNA (MB),\(^9\) and has been shown to be predictive to response to anti–PD-L1 therapy.\(^10\) In the CheckMate026 trial, which compared nivolumab to platinum-based chemotherapy as first-line treatment of NSCLC, OS did not differ between nivolumab and chemotherapy. A subgroup analyzed with TMB, as determined by whole-exome sequencing, indicated

<table>
<thead>
<tr>
<th>Pretreatment AR-V7–Positive</th>
<th>Pretreatment AR-V7–Negative</th>
<th>Pretreatment AR-V7–Positive</th>
<th>Pretreatment AR-V7–Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA ORR, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA PFS, mo (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS, mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Clinical or radiographic; PSA response is defined as ≥50% decline in baseline PSA maintained for 24 weeks.

Abbreviations: AR-V7, androgen receptor-variant 7; PSA, prostate-specific antigen; ORR, overall response rate; PFS, progression-free survival; NR, not reached; HR, hazard ratio; OS, overall survival; NA, not available.

<table>
<thead>
<tr>
<th>Pretreatment AR-V7–Positive</th>
<th>Pretreatment AR-V7–Negative</th>
<th>Post-Treatment AR-V7–Negative</th>
<th>Post-Treatment AR-V7–Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PSA PFS, mo (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**A** Portal 7 Detected by Quantitative Reverse Transcriptase Polymerase Chain Reaction in Circulating Tumor Cells as Both Primary and Acquired Resistance to Abiraterone and Enzalutamide

<table>
<thead>
<tr>
<th>Abiraterone (n = 31)</th>
<th>Enzalutamide (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment AR-V7–Negative</td>
<td>Pretreatment AR-V7–Negative</td>
</tr>
<tr>
<td>Patients, n</td>
<td></td>
</tr>
<tr>
<td>PSA ORR, % (95% CI)</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
</tr>
<tr>
<td>PSA PFS, mo (95% CI)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
</tr>
<tr>
<td>OS, mo</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td></td>
</tr>
<tr>
<td>p Value</td>
<td></td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Commercial Launch Date</td>
<td>June 2014</td>
</tr>
<tr>
<td>Amount of Blood Needed</td>
<td>Two 10-mL Streck tubes</td>
</tr>
<tr>
<td>Minimal Amount of Cell-Free DNA</td>
<td>&gt; 5 ng of cell-free DNA1</td>
</tr>
<tr>
<td>Methods for Isolating ctDNA</td>
<td>QIAamp circulating nucleic acid kit (Qiagen)</td>
</tr>
<tr>
<td>Types of Alterations Analyzed and No. of Genes</td>
<td>Complete exons (18 genes)</td>
</tr>
<tr>
<td></td>
<td>Critical exons (36 genes)</td>
</tr>
<tr>
<td></td>
<td>CNV (3 genes)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Sequencing Platform</td>
<td>HiSEquation 2500 (Illumina)1,2</td>
</tr>
<tr>
<td>Depth of Coverage</td>
<td>≥10,000× (average raw)</td>
</tr>
<tr>
<td>Single-Nucleotide Variation</td>
<td>Varies between &lt; 0.1% and 0.1%; depends on particular gene</td>
</tr>
<tr>
<td>Indel</td>
<td>Varies between &lt; 0.1% and 0.1%; depends on particular gene</td>
</tr>
<tr>
<td>CNV/Amplification</td>
<td>Varies between &lt; 0.1% and 0.1%; depends on particular gene</td>
</tr>
<tr>
<td>Fusions/Rearrangement</td>
<td>Varies between &lt; 0.1% and 0.1%; depends on particular gene</td>
</tr>
<tr>
<td>Turnaround Time for Results</td>
<td>Within 2 wk of receiving blood sample</td>
</tr>
</tbody>
</table>

Continued
### TABLE 8. Comparison of Various and Most Current Versions of Guardant360 and Foundation Medicine FoundationACT Liquid Biopsy Platforms (as of December 31, 2017) (Cont’d)

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<thead>
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<tbody>
<tr>
<td>ABL, CSF1R, ERBB4, FLT3, KDR (VEGFR2), PROC, RB1, and SMARCBI genes were deleted and replaced with ARAF, ARID1A, BRCA1, BRCA2, CCND1, CCND2, CCNE1, CDK4, CDK6, CDKN2B, ERK1, GATA3, MAP2K1, MAP2K2, NF1, NTRK1, NTRK3, NFE2L2, RHEB, RHOA, RIT1, RAF1, and ROS1 genes. Copy number amplification calling increased from 3 to 16 genes (added ARAF, ARID1A, BRCA1, BRCA2, CDH1, CDKN2A, CDKN2B, ERK1, RAF1, and RIT1) and 14 splice site variants was added.</td>
<td>RB1 and TSC1 genes were added; number of fusions detected increased from 4 to 6 (additional FGFR2 and FGFR3 fusion detection). Indel coverage for ERBB2 (exon 19/20) and MET exon 14 splice site variants was added.</td>
<td>SRC and CDKN2B were deleted from panel and DDR2, MAPK1 (ERK2), MAPK3 (ERK1), MTOR, and NTRK3 were added. Copy number amplification calling was increased to 18 genes (CCND1, CCND2). Indel coverage expanded from 3 to 23 genes (ATM, APB, ARID1A, BRCA1, BRCA2, CDH1, CDKN2A, CDKN2B, ERK1, RAF1, and RIT1).</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>References (Selected Clinical Use of One Particular Platform)</td>
<td>73-76</td>
<td>75-79</td>
<td>64, 75, 76, 80, 81</td>
<td>5,800 per test ($5,000 suggested contracted price per test)</td>
<td>$5,800 USD per test (contracted price may vary)</td>
</tr>
</tbody>
</table>

*Although the difference in the number of genes is 11 between the current Guardant360 and Foundation Medicine FoundationACT, the actual difference in the number of genes analyzed is 31 because of unique genes analyzed by each liquid biopsy. Twenty-one genes were unique to Guardant360: ARAF, ARID1A, ATM, FBXW7, GATA3, HNF1A, MAPK3, MLH1, MFI, NFE2L2, NOTCH1, NTRK1, NTRK3, RB1, RHEB, RHOA, RIT1, SMAD3, STK11, TSC1, VHL. Ten genes were unique to Foundation Medicine FoundationACT: ABL, BTK, CRKL, ERK1, FOXL2, MDM2, MYD88, PDGFR-beta, PD-L2, VEGF-alpha.

**The 19 genes that have complete exon coverage in the Guardant 73-gene panel are as follows: APC, ARAF, ARID1A, ATM, BTK, CRKL, CTNNB1, EML4, ERBB2, HRAS, KIF1B, KIT, MAP2K1 (ERK2), MAP2K2 (ERK1), MET, MYD88, PIK3CA, RAF1, TPS1, STK11. Underlined genes have complete exon coverage by Foundation Medicine FoundationACT.

†Both Guardant and Foundation Medicine FoundationACT report four common fusions: ALK, ROS1, RET, and FGFR3 fusions. Guardant360 also reports additional NTRK1 and FGFR2 fusions, and Foundation Medicine FoundationACT reports additional EGFR and PDGFR-alpha fusions. **ROS1 rearrangement is the only ROS1 alteration detected by the current version of Foundation Medicine FoundationACT.

Abbreviations: PPV, positive predictive value; NA, not available; USD, US dollars.
that patients with NSCLC and high TMB had a marginally significantly improved PFS compared with those receiving platinum-based chemotherapy (9.7 months [95% CI, 5.1 months to not reached] versus 5.8 months [95% CI, 4.2–8.5 months]; HR 0.62 [95% CI, 0.38–1.00]). OS did not differ between nivolumab and chemotherapy regardless of high or low TMB. Importantly, there is excellent concordance between TMB as determined by a commercially available (Foundation Medicine Inc.) tissue-based hybrid-capture NGS method and whole-exome sequencing of the tumor but essentially no correlation between TMB and PD-L1 expression.

It is now feasible to determine TMB by liquid biopsy using whole-exome sequencing or NGS hybrid-capture method. The blood TMB (bTMB) assay developed by Foundation Medicine Inc. uses 10 mL of plasma to deliver an account of somatic base substitutions down to 0.5% allele frequency across 394 genes from as little as 1% tumor content in a cell-free DNA sample. Computational methods differ: bTMB analyzes only single-nucleotide variants (SNVs), whereas tissue TMB also includes analysis of indels and fusions. Sensitivity, specificity, and positive predictive value were 93.9%, 100.0%, and 100.0%, respectively, when compared with tissue TMB. Importantly, the bTMB assay demonstrates strong sensitivity and specificity between the cut-points of 8–20 mutations/MB. The clinical utility of the bTMB assay was retrospectively analyzed in 783 patients with NSCLC receiving second-line therapy (OAK and POPLAR); PFS and OS were compared between atezolizumab (an anti–PD-L1 antibody) and single-agent docetaxel as second-line treatment. At a bTMB cutoff of 16 or greater, PFS and OS significantly improved in the phase II randomized POPLAR study. Among the 850 patients enrolled in the phase III OAK trial, 583 patients were considered as the “biomarkers evaluable population” (BEP) for bTMB. A bTMB of 16 or greater represented 43% of the BEP, and the sensitivity and specificity were both 100% when compared with tissue TMB. The bTMB assay is being validated in a global, multicenter, multicohort, randomized phase II/III trial without certain targetable driver mutations (RET or ALK fusion) detected based on blood-based assays; additionally, the trial is comparing single-agent atezolizumab therapy to standard of care based on bTMB results for those patients without RET or ALK rearrangement.

USE OF cTCDNA IN LIQUID BIOPSY TO DETECT MINIMAL RESIDUAL DISEASE IN SOLID TUMORS

Most solid tumors do not have a single truncal actionable driver mutation. There is vast literature on the use of non-specific cTCDNA in solid malignancies ranging from detection to monitor treatment response to detection of recurrence, and even for survival prognostication, all of which are beyond the scope of this review. However, cTCDNA detection by liquid NGS has been used to identify minimal residual disease (MRD); we review two important studies here.

In a study of 230 patients with resected stage II colon cancer conducted by Tie and colleagues, 20 (8.7%) patients had ctDNA detected by massive parallel sequencing. Most of these mutations were TP53, APC, and KRAS. There was no difference in clinicopathologic difference (age, sex, right-versus left-sided colon, tumor differentiation, T3 versus T4, number of lymph node resected < 12 versus ≥ 12, mismatch repair status, presence or absence of lymphovascular invasion, with or without adjuvant chemotherapy) between patients with and without detectable ctDNA. Among the 178 patients not treated with adjuvant chemotherapy, postoperative recurrence occurred in 11 of 14 (78.6%) ctDNA-positive patients compared with 16 of 164 (9.8%) ctDNA-negative patients. The 3-year relapse-free survival rate was 0% for ctDNA-positive patients compared with 90% for ctDNA-negative patients (HR 18; 95% CI, 7.9–40; p = 2.5 × 10−12). By multivariate analysis, ctDNA positivity (HR 28; 95% CI, 11–68; p = .0001) and T stage (T4 versus T3; HR 8.1; 95% CI, 3.1–21; p < .0001) were the two independent predictive factor for RFS after factoring in the above clinicopathologic factors. In addition, among the 230 patients, ctDNA positivity (HR 14; 95% CI, 6.8–28; p < .0001) and T stage (HR 2.6; 95% CI, 3.1–5.5; p = .001) remained the two independent factors for DFS after factoring in adjuvant chemotherapy. More importantly, postoperative elevation of CEA level was not a predictive factor for relapse-free survival, even by univariate analysis with or without adjuvant chemotherapy. Furthermore, cTCDNA positivity immediately after completion of postoperative chemotherapy was significantly associated with poor relapse-free survival (HR 11; 95% CI, 1.8–6.8; p = .001). However, the number of patients analyzed was 44, and only three patients had ctDNA positivity immediately after completion of postoperative chemotherapy.

Finally, during the follow-up period, ctDNA was significantly more frequently positive (23/27 [85%]) than was CEA elevation (11/27 [41%]) at the time of radiographic recurrence (p = .002). The time between ctDNA positivity (median, 167 days) was significantly longer than that between CEA elevation (median, 61 days) to radiographic recurrence (p = .04). This retrospective analysis of prospective collected data indicated that ctDNA monitoring has the ability to detect MRD and hence early recurrence, leading to the potential initiation and/or lengthening of adjuvant chemotherapy based on the presence or absence of cTCDNAs. There is a randomized cTCDNA driven adjuvant chemotherapy trial in resected stage II CRC in Australia/New Zealand (DYNAMIC,
Trial ID number: ACTRN12615000381583. In the standard-of-care arm, adjuvant chemotherapy will be given as determined by the clinicians, while in the investigational arm, adjuvant chemotherapy will be guided by the presence (adjuvant chemotherapy) or absence (no adjuvant chemotherapy) of postoperative ctDNA in resected stage II CRC. The primary endpoint is to evaluate whether an adjuvant therapy strategy based on ctDNA results may affect the number of patients treated with chemotherapy and recurrence-free survival.

TRACERx is a U.K. study that developed proprietary NGS technology to link the individual patient’s tumor DNA to plasma ctDNA by identifying two distinct tumor-associated mutations (usually SNV). The resected tumor was further microdissected at several different areas, and all “subtumors” underwent NGS sequencing to detect tumor heterogeneity. The TRACERx study group used this phylogenetic ctDNA (at least two SNVs) tracking to detect recurrence in 96 patients with resected early-stage lung cancer. A group of 24 patients were followed longitudinally with pre- and postoperative plasma ctDNA; of these, 10 had been relapse free for a median of 775 days, whereas 14 had confirmed relapse. Thirteen of the 14 patients who relapsed had ctDNA detected before or at clinical relapse compared with only one of 10 patients in remission (two SNVs). Overall, the median duration between ctDNA detection and radiographic evidence of relapse was 70 days. Relapse can involve one or more subclones. This analysis has some limitations due to lack of regularly scheduled imaging to account for potential lead-time bias of regular liquid biopsy compared with detection of recurrence by clinical practice. Regardless, the TRACERx approach remains an important technology that accounts for tumor heterogeneity in the primary tumor, especially because most lung cancers do not harbor a signature actionable driver alteration.

Detection of MRD may turn out to be the most important aspect of use of liquid biopsy because it may help guide extent of adjuvant treatment, similar to the use of Epstein-Barr virus load in the treatment of early-stage nasopharyngeal carcinoma.

**SHEDDERS VERSUS NONSHEDDERS OF ACTIONABLE GENOMIC ALTERATIONS**

In the TRACERx study, 46 of 96 patients had at least two SNVs that allowed phylogenetic ctDNA tracking, including 30 of 31 (97%) lung squamous cell carcinomas, 11 of 58 (19%) lung adenocarcinomas, and five of seven other NSCLCs. Among stage I NSCLC, 16 of 17 squamous cell carcinomas (94%) compared with five of 39 (13%) adenocarcinomas had detectable ctDNA. Of note, the median necrosis rate in lung squamous cell carcinoma (40%; n = 31) was significantly higher than in ctDNA-positive lung adenocarcinomas (15%; n = 11) and ctDNA-negative adenocarcinomas (2%; n = 47; p < .0001). Multivariate analysis indicated that nonadenocarcinoma histology (p = .001), lymphovascular invasion (p = .042), and high Ki-67 proliferation index (p = .022) are independent predictors of ctDNA positivity but not tumor necrosis (10% increment increase; p = .862), tumor size (1-cm increment increase; p = .134), or amount of ctDNA (p = .229). Importantly, the mean plasma variant allele frequency positively corresponded to tumor size. The TRACERx team was able to estimate that a mean clonal plasma variant allele frequency of 0.1% corresponds to a tumor burden of 10 cm³ or a burden of 302 million tumor cells.

A large-scale systemic review of 39 studies that included 4,052 patients, the detection of ctDNA was associated with a significantly worse OS in multivariable analyses [HR 2.70; 95% CI, 2.02–3.61; p < .001]. There was also a statistically significant association between high total cell-free DNA and worse OS at 3 years by multivariate analysis (HR 1.91; 95% CI, 1.59–2.29; p < .001). Thus, the use of liquid biopsy to identify shedders and nonshedders has important clinical implication and has been proposed to be included as part of the staging workup (tumor, node, metastasis, biopsy).

**CONCLUSION**

The advantages of liquid biopsy not only include the possibility to circumvent the need to achieve adequate tumor tissue biopsy specimens, it also reflects an aggregate of ctDNA output from potentially both primary and all metastatic sites accounting for tumor heterogeneity that cannot be evaluated by a single core tumor needle biopsy. Liquid biopsy may provide prognostic implication and help guide initiation and/or duration of adjuvant treatment by detecting MRD. Although all the current government-approved liquid biopsy test kits are designed to detect only mutations in one or a few specific genes, the future of liquid biopsy will be using NGS with increased sensitivity and ability to detect all modes of genetic alteration and TMB. The gene panel and limit of detection used by commercial NGS liquid biopsy kits change over time. It is incumbent upon the ordering physician to understand the current NGS platforms and performance characteristics and upon readers to interpret the literature with the comprehension of the changes in the gene panel and performance characteristics of commercial NGS tests as time goes by.

**References**


100. Mok TS, Gadgeel S, Kim ES, et al. 1383TiP. Blood first line ready screening trial (B-F1RST) and blood first assay screening trial (BFAST) enable clinical development of novel blood-based biomarker assays for
tumor mutational burden (TMB) and somatic mutations in 1L advanced or metastatic NSCLC. *Ann Oncol*. 2017; 28(suppl_5):mdx380.084.


Complexity of Delivering Precision Medicine: Opportunities and Challenges

Andrew A. Davis, MD, Amy E. McKee, MD, Warren A. Kibbe, PhD, and Victoria M. Villaflor, MD

OVERVIEW

Precision medicine has emerged as a tool to match patients with the appropriate treatment based on the precise molecular features of an individual patient’s tumor. Although examples of targeted therapies exist resulting in dramatic improvements in patient outcomes, comprehensive genomic profiling of tumors has also demonstrated the incredible complexity of molecular alterations in tissue and blood. These sequencing methods provide opportunities to study the landscape of tumors at baseline and serially in response to treatment. These tools also serve as important biomarkers to detect resistance to treatment and determine higher likelihood of responding to particular treatments, such as immune checkpoint blockade. Federally funded and publicly available data repositories have emerged as mechanisms for data sharing. In addition, novel clinical trials are emerging to develop new ways of incorporating molecular matched therapy into clinical trials. Various challenges to delivery of precision oncology include understanding the complexity of advanced tumors based on evolving “-omics” and treatment resistance. For physicians, determining when and how to incorporate genetic and molecular tools into clinic in a cost-effective manner is critical. Finally, we discuss the importance of well-designed prospective clinical trials, biomarkers such as liquid biopsies, the use of multidisciplinary tumor boards, and data sharing as evidence-based medicine tools to optimally study and deliver precision oncology to our patients.

TARGETED THERAPY

Through the years, there have been a number of success stories demonstrating the promise of targeted therapy in precision oncology. In several instances, particular drug regimens have demonstrated promise based on molecular targets across multiple histologies. For example, the tyrosine kinase inhibitor imatinib has demonstrated efficacy in both chronic myeloid leukemia with BCR-ABL fusion gene and tumors expressing c-kit in gastrointestinal stromal tumors based on blocking activated receptor tyrosine kinase activity, but no efficacy was reported in adenoid cystic carcinomas.
of the salivary gland expressing c-kit.1–3 As another example, the combination of trastuzumab with chemotherapy in patients with breast cancer, metastatic gastric adenocarcinoma, and salivary ductal adenocarcinoma with HER2 amplification improves clinical outcomes.2,5,6

In other histologies, targeted therapies against precise molecular aberrations have produced differing outcomes, suggesting a tissue- or microenvironment-dependent response or perhaps another factor that is either driving the malignancy or causing resistance to the treatment. For example, in melanoma, about 50% of patients have mutations in the BRAF gene, with the majority of these mutations occurring in the V600E domain. Vemurafenib and dabrafenib have demonstrated prolonged progression-free survival and overall survival in patients with BRAF V600E mutations in melanoma, leading to the approval of these drugs based on the phase III studies BRIM-3 and BREAK-3.7,8 However, the example of BRAF-mutated cancers has illustrated several other important points in precision oncology. First, molecular aberrations are often shared across multiple histologies, with BRAF-mutated tumors in nearly 15% of all cancers, including hairy cell leukemia, colorectal cancer, and lung cancers. Based on the results from basket trials, different histologies have vastly different response rates, complicating treatment assignment. For instance, in colorectal cancer harboring BRAF V600E, treatment with single-agent vemurafenib produced response rates of less than 10%, compared with the 57% objective response rate with melanoma.9,10 The mechanism for this difference in response is hypothesized to be mediated by EGFR signaling with patients with colorectal cancer having much higher level of EGFR expression relative to patients with melanoma. In a vemurafenib basket trial with an extension arm for previously treated patients with colorectal cancer, the safety and efficacy of vemurafenib combined with cetuximab, an anti-EGFR antibody, was assessed.11 Further data indicate vemurafenib may sensitize these tumors to cetuximab and produce responses in some patients with chemotherapy refractory disease. Therefore, BRAF was determined to be a relevant target, but only in the context of appropriate dual targeting after elucidation of the molecular pathway. The study by Hyman et al10 was also important in identifying NSCLC as a target for BRAF and later BRAF and mitogen-activated protein/extracellular signal–related kinase dual inhibition.

NSCLC is an example in which the presence of specific driver mutations is important for selecting targeted agents. Somatic mutations in EGFR, ALK, and ROS1 are often oncogenic and promote proliferation and survival in the absence of ligand binding. These mutations primarily occur in patients with adenocarcinoma, with a different frequency of mutations depending on geography (e.g., approximately 15% of white vs. approximately 50% in East Asian patients).11,12 Mutations in EGFR typically occur in exons 19 to 21, leading to a constitutively active kinase domain. The most common mutations include EGFR L858R in exon 21 and in-frame deletions in exon 19.13,14 EGFR-targeted therapies include erlotinib, gefitinib, afatinib, and osimertinib. The ALK inhibitors crizotinib, ceritinib, alectinib, and brigatinib have all been approved by the U.S. Food and Drug Administration (FDA) between 2011 and 2017. First- (crizotinib) and second-generation (ceritinib, alectinib, and brigatinib) ROS1 inhibitors (crizotinib) also are in clinical use. The success of EGFR-targeted therapies, in addition to ALK inhibitors and ROS1 inhibitors, has led to the recommendation of using genomic profiling for all patients with advanced NSCLC.15

**BIOMARKERS TO PREDICT RESPONSE TO THERAPY**

**Tools to Monitor Resistance**

Reliable biomarkers are a critical component of precision medicine to match the right patient with the right treatment at the right time. Clinically relevant biomarkers include genomic alterations in tissue or blood, circulating tumor cells (CTCs), gene expression assays, protein assays, and tools to predict response to immune checkpoint blockade, chemotherapy, targeted therapy, or radiation therapy. These tools are still being explored in their clinical potential.

In advanced malignancies, resistance to treatment is common after frontline therapy. For example, in EGFR-mutated NSCLC, resistance mechanisms to first-line EGFR-targeted therapies, with a mutation of a threonine 790 to methionine (T790M) in exon 20 being the most common. This resistance mutation restores the tyrosine kinase affinity to adenosine triphosphate and is one of several resistance mechanisms, including MET gene amplification, PIK3CA, and transformation into small-cell lung cancer.16 These targets are a very active area for drug development.

The question remains how best to identify mutations in patients with advanced malignancies. Traditionally, tissue biopsies have been used to establish the histology and tumor architecture at baseline. With improvement in sequencing technologies, comprehensive genomic profiling (CGP) of tissue has become the standard of care for sequencing across multiple tumor histologies. However, the practicality

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**PRACTICAL APPLICATIONS**

- **Precision medicine** aims to match patients with appropriate molecularly matched treatments.
- **Several examples** of targeted therapies have demonstrated considerable success, but this varies by molecular target and histology.
- **Biomarkers** are emerging to predict response to therapy, detect resistance, and select patients for molecularly driven or immune-checkpoint blockade as opposed to conventional chemotherapies or best supportive care. Additionally, some biomarkers may be beneficial to monitoring response, although this application still needs more data.
- **Data sharing** and regulatory science are critical components of precision medicine.
- **Analysis of tissue and liquid biopsies**, molecular tumor boards, and well-designed prospective trials are needed to move the field forward.

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of using tissue biopsies to monitor for mutations serially is limited due to patient discomfort and risk associated with repeat tissue biopsy and difficulty in capturing spatial tumor heterogeneity. Therefore, emerging data have demonstrated the feasibility of cell-free circulating tumor DNA (ctDNA) to detect amplifications, fusions, insertions, deletions, and point mutations with noninvasive blood draws. ctDNA has a relatively short half-life, ranging from approximately 16 minutes to 2.5 hours, and is detected in blood after it has been actively secreted or shed into the blood supply after a localized region of the tumor has become hypoxic, leading to apoptosis or necrosis.17

Multiple sequencing technologies have been used to detect genomic alterations or mutations, such as next-generation sequencing and digital-droplet polymerase chain reaction.18,19 The sensitivity and specificity depends on the technology and individual sequencing platform, and specificity, particularly at higher mutant allele frequencies, is quite high. The ongoing hypothesis is if mutations are detected in blood, treatment could be changed reliably based on the detection of known resistance mutations with potential for improvement in patient outcomes.20 Ongoing research is establishing optimal intervals and time frame of detection in relation to treatment, but lower sensitivity of particular assays may require confirmatory tissue biopsy, in some suspected cases, if no resistance mutations are detected in blood. Further research is needed to assess whether changing treatment based on alterations in blood prior to radiographic disease progression improves outcomes and the potential role and cost of incorporating ctDNA biopsies in the metastatic setting as a surrogate for tumor burden on imaging.

In breast cancer, approximately 70% of tumors express estrogen receptors. ESR1 is an example of an acquired mutation to endocrine therapy.21,22 This mutation results in estrogen-independent constitutive activation of the estrogen receptor, which results in acquired resistance to therapy by aromatase inhibitors. ESR1 mutations can be detected on CTCs and using ctDNA in approximately 25% to 39% of patients with acquired endocrine resistance. These mutations may predict response to other therapies. Potential exists to perform ex vivo testing of therapeutics based on isolation of CTCs, cells lines, establishment of patient-derived xenografts, or other models to explore next-line therapies. Future therapies and trials for targeting mutations with ESR1 mutations are in laboratory and clinical development. Beyond mutations, a growing body of literature has demonstrated the use of CTCs and ctDNA as prognostic and often predictive biomarkers for progression-free survival and overall survival, as well as a tool to identify disease recurrence and to monitor dynamic changes in real time.23

Biomarkers for Immune Checkpoint Blockade
Beyond targeted therapy, the field of immunotherapy has been observed across multiple tumor types, most notably melanoma, NSCLC, renal cell carcinoma, and bladder carcinoma. Early on, it was noted that tumors with a high mutagenic load had a higher proportion of patients who responded to immune checkpoint blockade. This led to the emergence of tumor mutational burden (TMB) as a biomarker for response to immune checkpoint blockade.24-26 TMB likely serves as a probabilistic indicator of neoantigens and potential immunogenicity. Importantly, this biomarker has been shown as an independent predictor across diverse cancers, suggesting that the marker may be tissue agnostic. Still, research is ongoing to identify whether particular histologies may have different TMB cut points and what algorithm is best used to quantify TMB as a predictor of neoantigen burden for cytotoxic T cells.

Mismatch repair (MMR) deficiency has emerged as another clinically meaningful biomarker. Based on a landmark phase II trial, PD-1 blockade with pembrolizumab demonstrated high immune-related objective response rates (ORRs) in patients with MMR-deficient colorectal cancer and non-colorectal cancers.27 In a more recent study, PD-1 MMR deficiency predicted response across 12 different tumor types of MMR deficiency with an ORR of 53% and complete responses in 21% of patients. This led to the approval of pembrolizumab as the first tissue-agnostic indication for MMR-deficient or microsatellite instability-high tumors in May 2017.28 Prior research has also demonstrated the association of microsatellite instability high predicting high TMB.29

NEXT-GENERATION SEQUENCING AND LANDMARK TRIALS
Improvements in sequencing technologies have revolutionized the accessibility of tissue CGP in clinical use. For example, current National Comprehensive Cancer Network guidelines recommend CGP in patients with advanced NSCLC adenocarcinoma.15 Across other histologies, clinical use of tissue CGP is more variable and controversial, depending on the particular tumor histology. With decreasing costs, there has been a shift in academic centers away from smaller, targeted panels with limited exon coverage toward in-house or commercial use of CGP, depending on the particular institution. The number of genes included in these panels continues to increase, and the use of RNA-sequencing and germline testing is expanding. Although there are clear success stories with known resistance mutations, general applicability of molecularly targeted therapy is more difficult.

The first randomized precision medicine trial, SHIVA, failed to demonstrate an improvement in progression-free survival using molecularly targeted therapies in heavily pretreated patients (2.3 months in the experimental group and 2.0 months in the control group).30 This trial has generated polarized viewpoints, with many suggesting that weaknesses in trial design may have masked potential benefits of a molecularly guided approach based on lack of combination therapy and some questionable molecularly targeted matches. In particular, monotherapy targeting mutations in the PI3K/Akt/mTOR pathway has been shown to have...
limited efficacy, and patients with mutations in this pathway accounted for a considerable proportion of the cohort. More recently, MyPathway and Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT) were published. The MyPathway study was an open-label (nonrandomized), phase IIa basket study that matched patients based on genomic alterations with targeted drugs for off-label use. Treatment arms included pertuzumab plus trastuzumab (HER2 overexpression/amplification), erlotinib (EGFR-activating mutations), vemurafenib (BRAF-activating mutations), or vismodegib (hedgehog pathway). Objective response rates were observed in 23% of patients (52 of 230), which included 48 partial responses and four complete responses in a heavily pretreated cohort. The key benefit of this basket design was to identify subgroups with notable responses, which in this cohort were metastatic HER2-overexpressing colorectal cancer (ORR 38%), salivary gland (80% ORR), and BRAF-mutated NSCLC (ORR 43%). At The University of Texas MD Anderson Cancer Center, the IMPACT trial reported over 1,000 patients with CGP, of which approximately 82% had detectable mutations. A total of 637 patients had at least one actionable alteration, with 390 (61%) treated with matched therapy and 247 (39%) with unmatched therapy. In the subset of patients treated with molecularly targeted therapy, response rate, progression-free survival, and overall survival were longer as compared with unmatched patients, with relative failure-free survival of 0.5 months and overall survival benefit of 1.1 months. There were some exceptional responders in the matched cohort. Multiple other trials are ongoing, with a representative sample of trials included in Table 1.

The promise of liquid biopsies to identify metastatic disease and best reflect spatial tumor heterogeneity has been an area of excitement for many years. In 2004, immunomagnetic sorting and detection of CTCs was established as having both prognostic and predictive roles in metastatic breast cancer using the FDA-approved CellSearch method (Menarini Silicon Biosystems, LLC). The finding now has been validated across other tumor types, including lung, prostate, colorectal, bladder, and kidney cancers. More recently, early evidence indicates the potential for CTCs to predict late relapse in hormone receptor–positive, HER2-negative stage II to III tumors prior to radiographic evidence of disease 5 years after diagnosis. Early work exploring the “omics” of single-cell CTCs has been published, with further work ongoing. ctDNA has emerged as another component of liquid biopsies as a quantitative marker of tumor DNA to reflect genomic alterations in blood. ctDNA detection varies by clinical stage and tumor type with greater than 75% of patients with

### TABLE 1. Representative Precision Medicine Trials

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<tr>
<th>Trial Name</th>
<th>Trial Abbreviation/Company</th>
<th>Distinctive Features</th>
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<tbody>
<tr>
<td>Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials</td>
<td>ALCHEMIST</td>
<td>Aims to improve outcomes using molecularly targeted or immune-based therapy in early-stage NSCLC</td>
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<tr>
<td>Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer</td>
<td>AURORA</td>
<td>Compares targeted gene sequencing and RNA sequencing on matched primary and metastatic samples</td>
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<tr>
<td>A Biomarker-Integrated Targeted Therapy Study in Previously Treated Patients with Advanced Non-Small Cell Lung Cancer</td>
<td>BATTLE-2</td>
<td>Uses biomarker-based tissue enrollment with adaptive randomization</td>
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<tr>
<td>Dual Anti–CTLA-4 and Anti–PD-1 Blockade in Rare Tumors</td>
<td>DART</td>
<td>Demonstrates feasibility to enroll patients with rare tumors quickly onto clinical trials</td>
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<tr>
<td>Identification of Men With a Genetic Predisposition to Prostate Cancer: Targeted screening in men at higher genetic risk and controls</td>
<td>IMPACT</td>
<td>Aims to screen a high-risk genetic group with known germline BRCA1 and BRCA2 mutations using an international cohort</td>
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<tr>
<td>Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer</td>
<td>I-SPY2</td>
<td>Uses an adaptive clinical trial design with novel design features aiming to decrease time, cost, and number of patients in phase II trials</td>
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<tr>
<td>A Study Evaluating Herceptin/Perjeta, Tarceva, Zelboraf/Cotellic, Erivedge, Alecensa, and Tecentriq Treatment Targeted Against Certain Molecular Alterations in Participants With Advanced Solid Tumors</td>
<td>MyPathway/Genentech</td>
<td>Reported high objective response rates in particular subgroups, including HER-2–amplified colorectal cancer and v-raf murine sarcoma viral oncogene homolog B1 V600-mutated NSCLC</td>
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<tr>
<td>National Cancer Institute-Molecular Analysis for Therapy Choice</td>
<td>NCI-MATCH</td>
<td>Uses a large-scale design with many treatment arms based on tissue tumor NGS sequencing</td>
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<tr>
<td>Molecular Targeted Therapy based on Tumor Molecular Profiling Versus Conventional Therapy for Advanced Cancer</td>
<td>SHIVA</td>
<td>Demonstrated a prospective randomized controlled trial design in precision oncology</td>
</tr>
<tr>
<td>Signature</td>
<td>Novartis</td>
<td>Incorporates large community enrollment with no limit to the number of enrollment sites</td>
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<tr>
<td>Targeted Agent and Profiling Utilization Registry Study</td>
<td>TAPUR</td>
<td>Uses FDA-approved agents off label to examine efficacy of these drugs in clinical practice</td>
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Abbreviation: NGS, next-generation sequencing.
advanced colorectal, pancreatic, breast, bladder, and melanoma compared with less than half of patients with brain and renal cancers. Potential clinical applications include detection of early disease relapse after surgery, monitoring response to therapy prior to radiographic progression of disease, and detection of resistance mutations. With the emergence of multiple commercial companies, turnaround time for sequencing has decreased, and costs likely will decrease to make serial sampling more accessible in clinical practice.

**ROLE OF DATA SCIENCE IN PRECISION MEDICINE**

Computing, data management, analytics, and associated disciplines have been transforming many industries and created a whole new economy. In 2017, the top five companies measured with cash on hand were all new economy companies—Apple, Microsoft, Alphabet (holding company for Google), Cisco, and Oracle. Thanks in part to these companies and the constant pace of innovation coming from the computing sector, we now have ubiquitous computing at our fingertips, and through pervasive connections to the internet, we have the “internet of things” that brings information to us and make sensor data available about us through many sources, including social media. Health care has been slow to adopt and slow to innovate to make effective use of these technologies. National challenges, like the presidential Precision Medicine Initiative, the National Strategic Computing Initiative, and the Beau Biden Cancer Moonshot have helped define a narrow, but informative path toward using data science, sensors, and devices to improve the health of the nation. This path highlights the importance of data sharing, the continued support of public data sets through open interfaces, resources that provide powerful but intuitive analytics, create a cancer research data ecosystem, encourage data reuse and software reuse, enhance validation and reproducibility, and lay the foundation for a cancer learning health system, in which the experience of every patient provides the evidence necessary for making data-driven health care decisions in oncology.

**Data Sharing and Repositories**

During the buildup to the signing of the 21st Century Cures Act that funded the Beau Biden Cancer Moonshot, then-Vice President Biden extolled the cancer community to share information more broadly and break down the existing silos that surround projects, organizations, and even consortia, as exemplified by his address at ASCO’s annual meeting in 2016. As cancer care and cancer research organizations, our ability to share clinical, genomic, imaging, and laboratory data are crucial to our ability to maximize our understanding of cancer and minimize the impact of cancer on tomorrow’s patients. Federally funded repositories, such as The Cancer Genome Atlas (TCGA), Therapeutically Applicable Research to Generate Effective Treatments, the data coming from CTD, ENCylopedia of DNA Elements, Model Organism ENCyclopedia of DNA Elements, and Genotype-Tissue Expression all contribute to the public cancer landscape. The International Cancer Genome Consortium has been an important international initiative that has engaged cancer researchers across the world in generating publicly available cancer genomic data. More recently, the American Association for Cancer Research project Genomics Evidence Neoplasia Information Exchange has brought many cancer organizations together to release clinical and genomic information publicly, through a collaboration with Sage Bionetworks and also through the National Cancer Institute–supported Genomic Data Commons (GDC). Other projects, such as the Department of Veteran Affairs’ Million Veteran Program and the National Institutes of Health “All of Us” Precision Medicine Initiative project, are contributing data about health and disease in the population. Together, these many projects are providing us with public data that opens a window into the intersection of genomics, population health, prevention, surveillance, treatment, and outcomes.

**Insights From Public Repositories**

TCGA has become the standard reference for variant frequencies in human tumors. In 2017, more than 1000 publications cited TCGA as a data source, and this number has been steadily increasing each year. As Genomics Evidence Neoplasia Information Exchange and other well-curated data sets such as the Multiple Myeloma Research Foundation COMMPass study become available publicly through the GDC, the ability to associate a given constellation of tumor mutations, clinical presentation, therapy, and patient outcomes becomes possible. Currently, much of the use of TCGA is to estimate variant frequency in a given tumor type and occurrence by race and ethnicity and examining variant co-occurrence. Other uses of TCGA, Therapeutically Applicable Research to Generate Effective Treatments, and many other data sets available either in Database of Genotypes and Phenotypes or the GDC include pathway analysis, correlation between imaging features (both pathology and radiology images available from The Cancer Imaging Archive), clinical phenotype, and proteomics (available from the Clinical Proteomic Tumor Analysis Consortium). Additional information on the prevalence of variants and classification of variants is available from cBioPortal, which has multiple current versions, including a version used to visualize data in the GDC. Likewise, ClinGen and ClinVar have been assembling information on variants present in both germline (inherited) and somatic tissues, including tumors. COSMIC provides an extensive, curated view of cancer somatic mutations, with COSMIC identification numbers used by many projects and clinical annotation pipelines to refer to a given somatic variant. MyCancerGenome, a resource developed at Vanderbilt University, provides both clinical synopses and lists potential targeted agents for mutations present in a given gene as well as available clinical trials relevant for the mutation.
Reuse and Reproducibility
Both reuse and reproducibility have gotten a lot of attention. Reuse, simply put, is the use of data, code, tools, or other research artifacts by groups other than those involved in generating, writing, documenting, and releasing those artifacts. For instance, protected data in TCGA have been accessed by thousands of investigators, and the openly accessible data have been accessed by many, many more. Release of data, code, and tools through standard resources, such as the GDC or Database of Genotypes and Phenotypes for data, Bioconductor and Galaxy for analysis packages, and GitHub for source code, promote data sharing and reuse. Adhering to good documentation standards, using tools like Jupyter Notebooks and Docker, and using well-defined Application Programming Interfaces, all contribute to lowering the barriers to reuse and collectively accelerate the pace of research. Reproducible science requires meticulous attention to all aspects of experimental design, experimental methods, reagents and protocols, and careful documentation and archival of experimental conditions, with care taken to document sources of variability to document systematic error, measurement error, biologic heterogeneity and variability, and analysis and interpretation bias. 71

REGULATORY SCIENCE: THE ROLE/CHALLENGES OF “SMALL DATA”
As precision medicine has segmented disease definitions into smaller populations, so have clinical trials enrolled smaller numbers of patients. For molecularly targeted agents that have a profound effect on a disease, this has not presented difficulties for marketing approval of new drugs and biologics. Trial designs that have supported marketing approval include both single-arm and randomized trials, and the FDA may use either accelerated approval, in which additional clinical trials may be required to verify and/or describe the clinical benefit, or regular approval, in which no further trials are required. Examples of products that were approved based on single-arm trials include: tisagenlecleucel, the CD19-directed autologous chimeric antigen receptor T cell, which was approved for the treatment of B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse based on a response rate of 83% complete responses/complete remission with incomplete blood count recovery in 63 patients; crizotinib, approved for ROS1-positive NSCLC based on a 66% ORR in 50 patients; and pembrolizumab, which was approved for the treatment of microsatellite instability-high or MMR-deficient solid tumors that have progressed following prior treatment and have no satisfactory alternative treatment options based on a 40% ORR in 149 patients across tumor types. 72-74

After a targeted therapy has gained marketing approval, any physician in the United States may prescribe it for any use. The FDA has no regulatory authority over whether a physician is prescribing a drug for an off-label use, which is considered the practice of medicine. However, prescribing a molecularly targeted agent for a tumor in which the target has not been clinically validated as an oncogenic driver or to have single-agent activity may lead to a patient deriving all of the risk of product side effects and no benefit. There are clinical trials to address this issue, the most relevant of which to address off-label use of approved targeted agents is ASCO’s Targeted Agent and Profiling Utilization (TAPUR) Study. This trial aims to evaluate molecularly targeted agents, which have received FDA approval in at least one indication and collect data on clinical outcomes, to inform potential additional uses of these drugs in indications not already approved by the FDA. As TAPUR uses only agents that already have FDA approval in at least one oncologic indication, this somewhat mimics what an oncologist may recommend for an individual patient whose tumor expresses a druggable target.

Single-patient Investigational New Drug applications allow access to therapies that are not yet approved for individual patients. A physician must apply to both the pharmaceutical company and the FDA for permission to use a product in a patient as well as obtain Institutional Review Board approval, under the assumption that the patient cannot be enrolled in any of the ongoing clinical trials for that product. Since 2009, the FDA has approved more than 99% of the requests for single-patient Investigational New Drug applications submitted to the FDA. 75,76 Similar to off-label use of approved targeted agents, use of a single-patient Investigational New Drug application to gain access to a targeted therapy for a patient whose tumor harbors a druggable biomarker offers an unknown benefit/risk profile.

CHALLENGES IN PRECISION MEDICINE AND WHAT IT MEANS TO THE SINGLE PATIENT
After the successes of imatinib, trastuzumab, and other targeted agents, the age of precision medicine was proclaimed. Over the last decade, although continued progress has been made across multiple tumor histologies and biomarker-based trials, important challenges remain. We outline several aspects of precision medicine that must be addressed to move the field forward.

First and foremost, tumor heterogeneity has presented a considerable challenge to matching patients with the right treatment at the right time. Numerous studies have demonstrated that the molecular features of tumors differ based on the location of tissue biopsies and between primary and metastatic sites. 77,78 Therefore, with tissue biopsies, there are inherent limitations of a single biopsy reflecting the genetic complexity of an advanced tumor and heterogeneity of the tumor microenvironment. To complicate matters further, expression of genomic alterations, such as EGFR in NSCLC, may differ across geographic populations, suggesting an additional level of genotype/phenotype/environment interactions.

Liquid biopsies have emerged as a theoretical tool to overcome spatial heterogeneity. Many concordance studies have been published in the literature with high specificity, but variable sensitivity when comparing tissue and blood biopsies. 79-82 Methodologic challenges exist when comparing across platforms containing different exon coverage with
different depth of sequencing. In addition, the time frame of collection in relation to therapy or progression may affect concordance results, particularly to detect low mutant allele frequency variants. More precise study designs and transparency in data sharing are necessary to move the field forward.

Furthermore, the more we sequence, the more genomic alterations we detect. Basket trials have demonstrated that drugs for patients with particular mutations vary across histology, indicating that tissue microenvironment that may mediate response and resistance. Beyond known driver mutations, many passenger mutations are detected, and strategies for optimal combination therapies are unknown. Because of the rapid evolution of both evidence and the presentation of CGP reports, it is difficult for physicians to keep up with the current genomically informed treatment guidelines and practices. Standardization of suggested treatments based on the latest level of evidence is very difficult to keep current. To compound this, patient understanding is often limited. Physician or midlevel provider time is necessary to explain the difference between germline and somatic alterations and explain how and which molecular alterations may be appropriate for treatment and to what extent changes in ctDNA warrant clinical progression or actionability. Molecular tumor boards to discuss genomic alterations in the context of prior treatment and current performance status have become more common, particularly at academic institutions. For these practices to become more uniform, there is a need to standardize and formalize the recommendations of molecular tumors boards, along with education and accessibility of tumor boards in the community.

Choosing an appropriate platform (tissue vs. blood) with an appropriate sequencing depth depends on clinical context. Many institutions are beginning to develop in-house panels, but a considerable proportion of CGP is performed by commercial next-generation sequencing platforms. With outsourcing of tissue and blood specimens, data sharing and transparency are critical. Many questions arise, such as defining the appropriate thresholds for calling particular genomic alterations or amplifications. How is TMB calculated by different commercial platforms? How should RNA-sequencing data be incorporated into research or clinical practice? How can institutions and practices best collaborate with industry to improve outcomes for our patients?

Ultimately, we must better define which patients should be tested or when the testing is most appropriate. In treating patients with advanced malignancies, there is an important balance between maintaining quality of life, while also matching patients with palliative treatments that optimally control disease progression, while also monitoring for therapy resistance. We hope that as further competition enters the marketplace, cost will continue to decrease, making serial sampling more accessible for our patients. Further evaluation is necessary to validate that targeting circulating biomarkers in the blood in advanced disease improves clinical outcomes.

From an individual patient perspective, the tendency is often “more is better” and “what else can be done” to help the patient feel better or live longer. Precision medicine has generated considerable and, at times, unreasonable, expectations in the popular press. With the expansion of clinically available genetic and molecular testing, along with direct-to-consumer marketing, patients often present to clinic with questions regarding utility of these tests and treatments. Each individual patient wants the best possible treatment and, in many cases, requests these tests to help guide treatment. Ultimately, it is the responsibility of the medical professional to stay well informed regarding appropriate circumstances to order precision medicine tests and recommend molecularly matched therapy. Furthermore, physicians must be prepared to discuss risks, benefits, alternatives, and implications of these results and treatments.

NEXT STEPS

Prominent opinion pieces in journals have questioned recent advancement of precision oncology in medicine. In some respects, these pieces paint a grim picture of the challenges of precision medicine. However, we see precision medicine as a step further down the road of progress, and, much like other areas of science, we must apply sound scientific methods to further advance the field.

First, we need well-designed, prospective, biomarker-based clinical trials. Novel clinical trial designs are underway or are completing. TAPUR, I-SPY2, NCI-MATCH, and DART are examples of collaborative efforts to design trials and accrue patients in new ways. Second, multidisciplinary molecular tumor board implementation is critical. As medical professionals, we are responsible for interpreting the tests that we order, and with rapid changes, collaborative teams are necessary to match patients with the optimal therapy. Third, formal educational programs reaching both academic and community physicians are necessary. In addition, educational tools for patients to understand these complex genetic data and to maintain the patient-physician relationship within the context of complicated, inference-based medical decisions are necessary. Fourth, a culture of data sharing and resources and repositories capable of supporting data sharing are needed to reduce the time from discovery to practice.

Precision oncology is not simply about matching patients with the appropriate targeted or immune-based therapy. Broadly speaking, it is about matching patients with the right therapy or withholding unnecessarily toxic therapy based on precise knowledge of the clinical and molecular features of the tumor. Therefore, this may encompass targeted therapy, immune-based therapy, or hospice if the tumor features and potential treatment side effects are not beneficial in the context of patient performance status. In summary, the field of precision oncology is continuing to evolve, much like the tumors in which we are applying these tools. We as a medical and scientific community must work together to best understand, study, and implement these tools for our patients.


The rapidly advancing therapeutic landscape in oncology is primarily reliant on the tremendous improvement in diagnostic tools and biomarkers for detecting cancer and specifically having the means to assess treatment response and detect adverse effects of treatment.\(^1,2\) The current gold standard in the case of solid tumors is the RECIST.\(^3-5\) RECIST was a guideline devised to standardize monitoring treatment based on imaging. The approach involves manually assessing differences in size of the target lesions on baseline and repeat CT scans (after therapy) to define various standardized categories\(^3,6\) of treatment response. However, even with modifications and refinements (Immune-Related Response Criteria \(\text{irRC}\)^7 and modified RECIST \(\text{mRECIST}\)^8), the current response evaluation criteria are limited, especially in the field of immunotherapy,\(^9,10\) because of the kinetics of tumor response to immuno-oncology treatment being unusual, with occasional radiographic progression as a result of inflammatory changes (pseudoprogression).\(^11-14\)

Early response assessment would help oncologists modify or change treatments tailored individually to each patient under therapy.\(^15\)

The aforementioned issues are especially critical and germane in the context of NSCLC, which makes up almost 85% of all lung cancers.\(^16\) NSCLC tumors have shown promising response to a multitude of treatment modalities, including a number of different experimental therapies. These include targeted therapies\(^17\) for common driver mutations, including \(\text{EGFR}^{,18} \text{ALK}^{,19}\) and \(\text{KRAS}^{,20,21}\). More recently, this has also come to include immune checkpoint inhibition therapy targeting the PD-1 receptor and its ligand, PD-L1.\(^22\)

Unfortunately, for most of these therapies, there is a lack of accurate prognostic and predictive biomarkers to identify which patients will respond to a specific therapy. For instance, tissue-based markers of PD-L1 expression,\(^23\) currently the gold standard for selecting patients for immunotherapy, have not been particularly predictive.\(^24\)

Consequently, there has been a push to develop and validate novel biomarkers and approaches for better characterization and prediction of tumor response. Specifically, there has been interest in developing tools to provide better objective characterization of clinical benefit from among multiple therapeutic modalities, tools that provide potentially superior and complementary information to currently used measures, like RECIST.

**RADIOMICS AS A NOVEL TOOL TO QUANTITATIVELY ANALYZE TUMOR IMAGING**

Radiomics is the high-throughput extraction of quantitative imaging features from a radiographic image. Specifically, there has been a great deal of interest in relating radiomic measurements of regions of interest on radiographic images (e.g., MRI and CT scans) with presence and aggressiveness of disease.\(^25,26\)

The field of radiomic analysis spans multiple approaches and modalities, including but not limited to computer-based
measurements of the (1) shape of the nodule involved in capturing the surface irregularities, reflective of the differences in tumor growth; (2) intratumoral texture, which is used to characterize the intranodular heterogeneity patterns; (3) peritumoral texture that involves capturing heterogeneity patterns at the nodular interface; and (4) semantic features, which are visually discernible features described by radiologists, like presence of emphysema and nodule location. Delta-radiomic features or difference in radiomic features obtained from pre- and post-treatment scans are now being evaluated as a complement to RECIST for monitoring therapeutic response, with delta-radiomic features potentially being able to reveal subtle changes in the tumor that precede size or volumetric changes.27 Other features that have been recently shown to be promising include vessel tortuosity28 and three-dimensional volumetric features.29

Depending on the types of radiomic texture filters used (e.g., Gabor,30 Laws,31 Haralick,32 or Co-occurrence33,34), several features potentially being able to reveal subtle changes in the tumor that precede size or volumetric changes.27 Other features that have been recently shown to be promising include vessel tortuosity28 and three-dimensional volumetric features.29

Within the oncology space, radiomics has found applications as a means of diagnosis, a prognostic tool predicting response to therapy50 across organ systems, including but not limited to brain,36-39 head and neck,40-42 breast,43-50 lung,42,51-53 prostate,54-58 rectum,59-64 and liver.65-69 In the context of lung cancer, radiomics has successfully allowed detection of malignancies in screening CT scans,13 provided a means to differentiate between benign and malignant lesions,51 enabled the prediction of risk of recurrence post-therapy,52 and provided a means to noninvasively assess response to therapy70 as well as helped to identify patients who would most benefit from therapy.28

**Radiomic Framework for Lung Cancer**

In the context of lung cancer, radiomics represents a possible exciting complement to RECIST for monitoring therapeutic response on longitudinal serial imaging scans as well as helping to predicting response to treatment from baseline radiographic images. One of the most important advantages for radiomics is that it can be potentially integrated into the normal clinical workflow without being disruptive.

The underlying process of radiomic analysis can be broadly categorized into the following main categories: (1) image acquisition and preprocessing, (2) identification of the volume of interest, (3) feature extraction and selection of most discriminating features, and (4) use of the selected features to build a classifier to predict the outcome of interest. These modules are briefly described here below.

**Image acquisition.** CT scans are the most commonly used diagnostic modality for identifying malignancy in a patient suspected to have lung malignancy.71 CT scans are also used in conjunction with the RECIST guidelines by radiologists and clinicians to monitor response to treatment as a function of changes in tumor volume. Current recommendations also suggest the use of low-dose CT (LDCT) as a means of screening in selected vulnerable populations. Radiomic analysis, meanwhile, is routinely done on noncontrast CT scans, because contrast can obscure the radiomic textural features.72 However, He et al73 found that the radiomic prediction accuracy in differentiating between benign and malignant nodules using intratumoral texture features only had a 5% difference in areas under the curve (AUCs; AUCnoncontrast was 0.75; AUCcontrast was 0.74).

One of the major limitations in quantitative image analysis and radiomics, however, is the wide variability and lack of uniformity across institutions, scanner platforms,74 slice thickness,75 reconstruction kernels,76 other acquisition parameters, and even nodule segmentations.9,77,78

He et al73 showed that the CT radiomic features to differentiate benign versus malignant nodules obtained on a thin slice (1.25 mm) performed better than those obtained on a thick slice (5 mm) with AUCnoncontrast of 0.75 versus AUCcontrast of 0.725 in an independent validation cohort (120 patients) of patients with solitary pulmonary nodules. On the same cohort, radiomics on a standard convolution kernel performed better (AUC of 0.725) compared with lung convolution kernel-based CT scan (AUC of 0.686). Mackin et al74 compared radiomic feature variability across four different CT scanner platforms (Siemens, Philips, GE, and Toshiba) and found that the interscanner variability of features was large relative to the interpatient variability for a case of 20 patients with NSCLC.

**Identification of the volume of interest and nodule segmentation.** The reconstructed images are ported into open source software that allows expert radiologists to place a boundary or a designated marker around the designated region of interest across the various slices where it appears. The identification of the volume of interest is first and the key

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**PRACTICAL APPLICATIONS**

- Quantitative imaging biomarkers are urgently needed to move beyond tumor response evaluation by RECIST because of its widely acknowledged limitations.
- Radiomics or computer-extracted novel imaging features from radiographic images have shown accuracy as a prognostic tool across the oncology space by identifying high-risk patients from low-risk ones.
- Precision cancer therapy is another area where radiomics could enable personalization of therapy based on each tumor’s unique radiomic signature.
- Radiomics on pretreatment images has shown promising results in also identifying patients that will respond to therapy and those that may not across various treatment modalities, including surgery, chemotherapy, immunotherapy, and molecular-targeted therapy.
- Delta-radiomics on serial radiographic images could serve as an effective and noninvasive way to assess effectiveness of therapy as well as predict early treatment response.
step in additional radiomic analysis. Manual identification by a radiologist is the current gold standard in radiomic analysis. Additionally, quantitative techniques are being developed to identify regions with their own unique physiology on radiographic images by combining various imaging modalities.79

Meanwhile, nodule segmentation involves the process of separating the nodule from the entire CT scan and is often the most critical part of the radiomic feature analysis pipeline.59 This is primarily because a number of the radiomic parameters are extracted from the segmented volume itself. Manual annotations remain the gold standard in nodule segmentation, but semi-automated segmentation methods, often with a final check by a radiologist, have also been used as a means of establishing the “gold standard” for nodule boundary.60,80,81 With interobserver variability being reported to be present in manually segmented tumors,81,82 another (potentially more cumbersome) approach is to try to average or aggregate delineations from multiple individual readers.66

Feature extraction. The different radiomic feature types are described below.

Semantic features. These are characteristics of the tumor as described by the radiologist during the analysis of the image. These features tend to be more resilient to variations in scanner and acquisition parameters but suffer from subjective evaluation and interobserver variability.35,66 Some of these features include the location of the lung nodule, presence of emphysema, effusions, ground glass opacities, features in the lung parenchyma, nodule attenuation, and nodule marginal patterns.72

First-order statistical features. These features relate to statistical moments within the volume of interest and are calculated across the voxel intensities within the CT image. These statistics include energy, entropy, kurtosis, skewness, standard deviation, mean, median, range, and variance. For example, the standard deviation and variance reflect the degree to which the gray levels vary from the mean in the histogram. Kurtosis, meanwhile, measures the degree of histogram sharpness, whereas skewness reflects the asymmetry associated with the intensity distribution.83

Shape and volumetric features. These features include margins, volume, minimum and maximum diameters, and surface area of the nodule; nodule volume was previously shown to be a predictor of therapy response.77,84,85 Shape features include width, height, depth, perimeter, area, eccentricity, compactness, radial distance, roughness, elongation equivalent diameter, and three-dimensional sphericity of the nodule.29,51,57 Other features include three-dimensional shape and margin sharpness.86,87

Texture features. These are second-order and higher-order statistical measures to identify spatial and architectural relationships between the intensities of voxels in the area of interest. They are used to assess heterogeneous enhancement, a hallmark of malignant tumors. Below are some of the classes of texture features used for lung nodule characterization on CT scans.

Local binary patterns. The local binary pattern feature vector involves dividing the area of interest into an array of pixels, each with a binary label. In each 3 × 3 matrix of pixels, the center pixel is compared with each of its neighboring eight pixels, and a binary value reflecting whether the center pixel is less or greater than the neighboring pixels is converted into a binary vector. Han et al68 showed the utility of local binary pattern radiomic features in distinguishing benign from malignant lung nodules on CT scans.

Gray-level co-occurrence matrices. First described by Haralick and Shanmugam72 in conjunction with remote sensing image analysis in satellite data and eponymously called Haralick features, this class of features has been among the most popular set of radiomic measurements used in diagnosis, prognosis, and prediction of treatment response for NSCLC.52,88 Using higher-order statistics, these features provide information related to the spatial distribution and the relative position of various gray levels throughout the image.49

Laws’ texture energy measures. Described by Laws,81 the texture energy approach measures the variations within a fixed window size. A set of nine 5 × 5 local texture masks is used to detect various texture types and then subsequently combined to calculate the texture energy. This is represented by a vector of nine numbers, each with a different texture attribute for the pixels analyzed. In a radiogenomic study,80 the Laws’ feature descriptor was also found to be the only radiomic feature descriptor to be significantly predictive for EGFR mutation (AUC of 0.67, p = .03).

Edge features. These include Sobel91 and Canny92 filters, which determine the density and direction of the edges in the image as a means to characterize the texture patterns. Edge detection methods have been used for lung nodule detection and segmentation from CT scans.93

Wavelet features. These provide a way to capture multiscale attributes across multiple different frequencies and wavelengths. These include the following attributes described below.

Fourier transforms. This class of features involves calculating the contour of the tumor by evaluating the frequency and interval with which the tumor contour and margin change. This is accomplished by representing these changes as a wave with amplitude and frequency that can be modulated to reflect different degrees of feature granularity in the image.94

Gabor filter. Named after Dennis Gabor and first used to describe the representation of an image in the visual cortex,95 the Gabor filters seek to capture gradients across different wavelengths and orientations.30,94,96 Gabor filters of various scales and rotations have been previously used to characterize textural patterns within the intratumoral and peritumoral spaces.38,43

Co-occurrence of local anisotropic gradient orientations. The co-occurrence of local anisotropic gradient orientations radiomics descriptor (recently introduced in33) attempts to capture the entropy or disorderliness in pixel-level gradient orientations. Specifically, co-occurrence of local anisotropic gradient orientations has been shown to enable discrimination between treatment-related changes and disease recurrence on MRI scans and also distinguish between benign and malignant nodules on CT scans.37,38,43
**Vessel tortuosity features.** Ailou and colleagues\(^{28}\) first reported significant differences (AUC, 0.79, \(p < .01\)) in computer-extracted tortuosity of tumor-specific vasculature on non-contrast CT scans. Specifically, the study reported differences in vessel tortuosity between patients with NSCLC who did and did not respond to immunotherapy using nivolumab. Novel features extracted from the vessels supplying the tumor involved quantifying three key attributes: (1) torsion, (2) curvature, and (3) branching statistics and patterns. This feature seems to exploit the fact that increased angiogenesis tends to be observed in more aggressive tumors, leading to more tortuous vasculature.

**Feature selection.** The massive number of computed radiomic features results in the so-called “curse of dimensionality,” an issue where the number of features is much larger compared with the number of training instances. One of the ways to accomplish this is by capping the number of selected features with the number of training instances. One of the top-ranked features is important criteria in picking features. For instance, to predict recurrence as an outcome, the chi square test would calculate the chi square coefficient between a feature variable and the recurrence outcome (recurrence labeled as one and no recurrence labeled as zero). Similarly, the Fisher exact test assigns high rank to features that have higher variance, whereas the Wilcoxon rank sum test selects features that are highly statistically significant in rejecting the null hypothesis (i.e., there were measurable differences between the cause and effect being studied; e.g., studying the relationship between treatment outcome and overall survival).**

**Univariate algorithms.** These include chi square test,\(^{100}\) Fisher exact test,\(^{101}\) and Wilcoxon rank sum test,\(^{102}\) which involve comparing the association between the features and the chosen outcome variable to identify the most predictive features. For instance, to predict recurrence as an outcome, the chi square test would calculate the chi square coefficient between a feature variable and the recurrence outcome (recurrence labeled as one and no recurrence labeled as zero). Similarly, the Fisher exact test assigns high rank to features that have higher variance, whereas the Wilcoxon rank sum test selects features that are highly statistically significant in rejecting the null hypothesis (i.e., there were measurable differences between the cause and effect being studied; e.g., studying the relationship between treatment outcome and overall survival).**

**Multivariate algorithms.** Multivariate models solve the issues with univariate analysis by not only measuring feature associations with the chosen outcome but also, helping to address the interfeature associations. Multivariate models, which are used in radiomic analysis, include minimum redundancy maximum relevance,\(^ {103}\) joint mutual information,\(^ {104}\) and variable importance on projection measure for principal component analysis (PCA-VIP)\(^ {105}\) to select the top features. For example, minimum redundancy maximum relevance helps to identify features that are not only discriminative but also, largely uncorrelated.

Other than discriminability, robustness and stability of the top-ranked features are important criteria in picking features. Various measures have been used to assess feature stability, including relative standard deviation,\(^ {26}\) intraclass correlation coefficient,\(^ {106}\) coefficient of variability,\(^ {107}\) and latent and preparation-induced instability score.\(^ {56}\) The availability of the National Cancer Institute–sponsored RIDER-CT data set, which comprises CT scans of patients with NSCLC taken 15 minutes apart, has also allowed for identification of those features that do not dramatically change between the test-retest scans.

**Constructing a classifier.** There are primarily two different classification approaches, supervised and unsupervised, which in conjunction with the top identified features, can be used to predict the probability of an event or the outcome of interest.

**Supervised classification models.** The supervised model is trained using a set of labels that represent the category of interest (e.g., differentiating between benign and malignant lung nodules or between responders and nonresponders). These approaches include support vector machines,\(^ {108}\) random forest classifiers,\(^ {109}\) linear discriminant analysis,\(^ {110}\) quadratic discriminant analysis,\(^ {111}\) and Adaboost.\(^ {112}\)

**Unsupervised model.** In some instances, the outcome labels are not explicitly known. These scenarios are amenable to unsupervised clustering. This approach involves first clustering the given features into different categories without any predefined labels, with the goal being to discover the hidden categories. Unsupervised classification approaches have also been used recently in predicting treatment response in NSCLC.\(^ {113-115}\) Clustering methods can include hierarchical, Bayesian, and partitioning-based approaches.\(^ {116,117}\) In addition, unsupervised clustering might also be useful in evaluating the utility of the selected features, even with known outcome labels. If the most discriminating features fail to stratify the patients into the given outcomes of interest, it might call into question if the features are, in fact, suitable for predicting the chosen outcome of interest.

**Analysis of the model performance.** Performance of radiomic and delta-radiomic features in the context of supervised classification methods is typically done via a receiver operating characteristic curve obtained by plotting the true-positive rate against the false-positive rate while continuously varying the decision threshold. The results are then reported as the AUC, with a higher AUC reflecting higher classification performance. Other performance measures include accuracy, reliability, sensitivity, specificity, and true and false predictive rates. When using unsupervised approaches, like clustering, it becomes more complicated to evaluate performance without the presence of ground truth labels. External validity measures\(^ {118,119}\) exist to evaluate clustering quality, evaluating how well the clustering matches the gold standard. These include purity, normalized mutual information, Rand index, and F measure. Internal quality criterion measures\(^ {120}\) include attaining a high intracluster similarity and a low intercluster similarity. Survival analysis is often a secondary measure reported to evaluate the performance of the prediction model using Kaplan–Meier and Cox proportional hazard analysis models\(^ {121}\) to predict measures, like overall survival, disease-free survival, and progression-free survival.

**APPLICATIONS OF RADIOMICS IN LUNG CANCER TREATMENT RESPONSE**

Radiomics studies in the lung cancer space encompass both predicting response to therapy and monitoring response to a particular treatment. Below, we describe applications of radiomics in the context of radiation oncology and chemotherapy as well as immune checkpoint inhibition therapy.
Radiation Oncology

In the radiation oncology space, radiomics is being shown to have substantial potential as a key noninvasive monitoring tool. Huynh et al\textsuperscript{27} showed that radiomic shape and tumor heterogeneity features from respiratory-gated CT scans enabled the prediction of treatment response to stereotactic body radiation therapy in patients with early-stage NSCLC. Also, Huynh et al\textsuperscript{21} used a principal component analysis feature selection algorithm to choose the most stable and discriminative features and built a multivariate model to predict response to stereotactic body radiation therapy in patients with NSCLC. Wavelet and textural features were found to be overexpressing in patients with distant metastasis (confidence interval of 0.67) that failed stereotactic body radiation therapy, whereas clinical and conventional parameters failed to be predictive in these patients. Meanwhile, Mattonen et al\textsuperscript{24} showed the significance of radiomic textural features, including gray-level co-occurrence matrices and gray-level features, which were intensified in patients who recurred even after radiation therapy in early-stage NSCLC. The radiomic features were predictive of recurrence (AUC of 0.85) after radiation. In contrast, six physician observers had a kappa value of 0.54 in predicting recurrence versus no recurrence in these patients. Coroller et al\textsuperscript{1} showed that radiomic wavelet features successfully predicted pathologic complete response in patients treated with chemoradiation alone in a cohort of 127 patients, whereas Jain et al\textsuperscript{25} found that radiomic textural features predicted pathologic complete response in 90 patients who underwent trimodality therapy using baseline CT scans. On an independent validation set of 45 patients, they obtained an AUC of 0.78 using a random forest-derived classifier comprising both intratumoral and peritumoral textural patterns. Fave et al\textsuperscript{23} showed that changes in radiomic intensity and texture features (delta-radiomics) from serial CT scans of patients with stage III NSCLC before, during, and after radiation therapy were strong indicators of tumor response to radiation therapy.

Chemotherapy

Rakshit et al\textsuperscript{126} showed that Haralick and Gabor textural features within the tumor were found to be overexpressed in patients who responded to pemetrexed chemotherapy in locally advanced NSCLC, and the radiomics predictor yielded an AUC of 81.33% on a blinded and independent validation set (22 patients). By including computer-extracted shape features, the AUC further improved to 83.44%. Interestingly, the most stable and discriminative features were obtained from the space immediately adjacent to the tumor (peritumoral space). Biologically, the peritumoral space is represented by the tumor microenvironment, which has been shown to be increasingly vital in characterizing tumor aggressiveness and the corresponding immune response.\textsuperscript{127} The increase in textural heterogeneity in the peritumoral region in chemotherapy responders can possibly be explained by subvisial microfibrosis as a result of chemotherapy response.

Immunotherapy

Low response rates (20%–40%) have been noted with immune checkpoint inhibitor drugs, even in patients having tissue-based high PD-L1 expression,\textsuperscript{22,128-129} the current gold standard in predicting response to immune therapy. Considering the gamut of adverse effects\textsuperscript{130-132} that these drugs might potentially cause, radiomics from baseline CT scans is being explored as a biomarker for treatment response. Radiomic features pertaining to vessel tortuosity extracted from baseline pretherapy CT scans have been recently identified as a potential independent predictor of response to Nivolumab in locally advanced NSCLC.\textsuperscript{28} Alilou and colleagues\textsuperscript{28} devised a novel radiomics descriptor to characterize the changes in the tumor microenvironment using vessel tortuosity metrics. In the training cohort (33 patients), the top three extracted vessel tortuosity features from pretreatment CT scans most predictive of outcome (responders vs. nonresponders determined clinically) were identified and then used for training a support vector machine classifier. The maximum curvature (f1), standard deviation of the torsion (f2), and mean curvature (f3) of the nodule vasculature were identified as the most discriminating features. Figures 1 and 2 illustrate the changes in vascular tortuosity for an IO responder and a nonresponder between pre- and post-treatment IO (2 weeks after the first cycle). The area (AUC) was 0.84 for the training and 0.73 for the test set (28 patients). Delta-radiomic features of changes in intra- and peritumoral heterogeneity were leveraged by Xie et al\textsuperscript{70} using serial CT scans (pre- and post-treatment), which in turn, enabled early identification of early responders in 41 patients with NSCLC treated with Nivolumab. Tang et al\textsuperscript{133} presented an NSCLC radiomic signature using unsupervised classification approaches. Using tissue-based CD3 count and PD-L1 expression in an early-stage NSCLC cohort, they generated four distinct cohorts using a combination of CD3 and PD-L1 low/high expressions. Haralick texture features and intensity measures were used to correlate radiomics expression with these four clusters, and corresponding survival analysis was carried out. Multivariate survival models indicated the highest overall survival in the radiomic cluster that was strongly correlated with high CD3 and low PD-L1 expressions.

CONCLUSION

In this article, we discussed the exciting and innovative space of radiomics and quantitative imaging techniques as a means to predict response to radiation therapy, different chemotherapeutic modalities, immune checkpoint inhibition treatment, and trimodality therapy as well as a prognostic indicator for early treatment response for these multiple regimens. These techniques and developments have shown tremendous promise in various domains, including recent explorations and forays in the expanding fields of immunotherapy and targeted and molecular therapy in oncology. These novel imaging techniques have also shown better accuracy in monitoring treatment response compared with current RECIST-based guidelines.
We briefly overviewed the radiomic framework with a brief discussion about the various types of radiomics feature descriptors in use and selection of the most stable and discriminative features, and we constructed a predictive classifier and evaluated the performance of the developed model in predicting the outcome of interest as well as analyzing survival data. We also discussed how it could be seamlessly integrated into the clinical workflow with minimal disruption. We also spoke about the morphologic and histogenomic underpinning behind many of these computer-extracted features to provide a more intuitive reasoning behind its prediction capacity.

We also noted that the existence of a large number of sources of variance remains an impediment to accurate radiomic analysis. In conjunction with relatively small data sets and mostly retrospective analysis, these sources are some of the limitations that it needs to actively overcome. The development of new techniques to alleviate this variation needs to be validated in large-scale multisite and multi-institution prospective validation studies to confirm its usefulness. The groundwork, however, has been laid, and the time is opportune for radiomics to be tested as a biomarker in prospective cohort studies and randomized clinical trials. It is only after successful validation in large-scale trials that radiomics can be accepted as a part of routine clinical practice.

To be part of the routine clinical decision-making system, radiomics needs to be a joint collaboration of oncologists, radiologists, physicians, and computational scientists. We hope that this overview will help clinicians better appreciate the field of radiomics, especially its potential in playing an important part in predicting treatment response and monitoring ongoing therapy.

**ACKNOWLEDGMENT**

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Fund; and the Wallace H. Coulter Foundation Program in the Department of Biomedical Engineering and the Clinical and Translational Science Award Program at Case Western Reserve University.

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Tumor Response Assessment for Precision Cancer Therapy: Response Evaluation Criteria in Solid Tumors and Beyond

Mizuki Nishino, MD, MPH

OVERVIEW

Objective assessment of tumor responses and treatment results has been the basis for the advancement of cancer therapies, and imaging plays a key role to provide a “common language” to describe the results of cancer treatment. Although Response Evaluation Criteria in Solid Tumors (RECIST) has been the most widely accepted method for assessing tumor response in the past decades, the limitations of RECIST have increasingly been recognized, especially with the recent advances of precision-medicine approaches to cancer. This article reviews the current concept of tumor response evaluations based on RECIST, describes the limitations of RECIST, and proposes strategies to overcome the limitations. The article emphasizes specific limitations in the setting of precision cancer therapy and cancer immunotherapy and discusses the important insights provided by the cutting-edge investigations in the emerging fields.

Evaluation of tumor response to therapy and incorporation of the results in the practice of clinical oncology provide the basis for advances in cancer treatment. Imaging plays a critical role for objectively characterizing tumor response to therapy and defining trial endpoints for novel agents. RECIST, introduced in 2000 and revised in 2009, has been widely used as a standardized method for tumor response assessment in the past two decades and has provided the basis for regulatory approvals for novel cancer therapy.

CURRENT METHOD OF TUMOR RESPONSE EVALUATION USING RECIST

RECIST version 1.1 (RECIST1.1) is the current version and is used as tumor response criteria in most trials of solid tumors in general. RECIST1.1 uses unidimensional diameters of target lesions and the sum of measurements of all target lesions as a quantitative measure of tumor burden (Table 1). Changes of the quantitative tumor burden are assessed in reference to the specific cutoff values in order to assign categorical response groups. In addition, qualitative assessment is performed for the changes of nontarget lesions and appearance of new lesions, which helps to define progressive disease (PD; Table 1).

GENERAL LIMITATIONS OF RECIST-BASED APPROACHES

Although RECIST provides a practical method for tumor response evaluations that are widely accepted as a standardized measure, the limitations of RECIST have been acknowledged. Major limitations that universally affect the assessment results regardless of tumor types or agents include variability of tumor size measurements and tumoral heterogeneity, both within a lesion and among different lesions in a patient. Measurement variability is an inherent limitation of quantitative imaging methods, including RECIST. Erasmus and colleagues evaluated measurement variability of 40 lung tumors and reported a 30% misclassification rate for progressive disease by RECIST; this finding indicated that nearly one third of patients can be classified as having PD because of the measurement variability rather than true tumor growth. Zhao and colleagues evaluated same-day repeat CT scans of 32 patients with non–small cell lung cancer (NSCLC) and reported the 95% limits of agreement of tumor size measurements ranging from (−18.3%, 15.5%) to (−22.8%, 23.0%). Another prior study assessed 43 patients with advanced NSCLC and demonstrated that RECIST1.1 was more reproducible with a narrower 95% limits of interobserver agreement (−18.6%, 25.4%) compared with those of the original RECIST (RECIST1.0). These observations indicate that RECIST is reproducible in reference to the partial response threshold (≥ 30% decrease); however, the cutoff for progression (≥ 20% increase) can be within the range of measurement variability and may misclassify patients as having PD because of measurement errors.

Of note, the measurement variability has more influence on the response assessment results in patients with smaller tumor burden because the response categories are...
defined by the proportional changes of tumor measurements. For example, a 3-mm difference in size because of measurement variability contributes to only a 6% difference in proportional change for a tumor measuring 5 cm on the reference scan but results in a 30% difference for a tumor measuring 1 cm on the reference scan; thus, in the latter case, it may affect the change in response category assignment. The issue is particularly relevant in patients treated with effective targeting therapy, who often demonstrate marked initial size decrease in their tumors. In these patients, the smallest tumor burden after response, or nadir, serves as a reference to define subsequent progression, and an increase of only a few millimeters may result in a 20% or greater increase compared with the nadir. To address this limitation, RECIST1.1 requires at least a 5-mm absolute size increase compared with the nadir to define PD, in addition to the 20% or greater increase that has been conventionally used in RECIST1.0 (Fig. 1). However, two prior studies evaluated the impact of the addition of the 5-mm rule in RECIST1.1 in patients with advanced NSCLC treated with EGFR inhibitors and demonstrated that only a minority of patients (6% [4 of 70] in one study and 1% [one of 104] in the other study) had longer time to progression because of the 5-mm requirement; this indicates the need for additional strategies, including more accurate and less variable measurement methods, to overcome the issue.

RECIST simply relies on unidimensional tumor size measurements for quantification of tumor burden, assuming that three-dimensional tumor volume burden is related to a planar measurement. However, in real life, tumors are heterogeneous in terms of growth rates and patterns within the same lesion (Fig. 2), or among different lesions in one patient, where some lesions increase whereas others remain unchanged or decrease during therapy. One of the approaches to address this issue, at least in part, is to apply tumor volume measurements to quantify entire tumor burden as a marker for treatment benefit and prolonged survival. The clinical application of the multi–detector row CT technology in the past decades has enabled volumetric acquisition of large anatomic volumes with isotropic voxels, allowing the segmentation and measurement of tumor volumes using high-resolution multi–detector row CT data (Fig. 3). Studies to date have consistently shown that

### TABLE 1. Summary of RECIST1.1 Guidelines for Tumor Response Assessment

<table>
<thead>
<tr>
<th>Components</th>
<th>Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement method</td>
<td>Longest diameter for nonnodal lesions except for lymph nodes; short axis for lymph nodes</td>
</tr>
<tr>
<td>Measurable lesion</td>
<td>Longest diameter of ≥ 10 mm* for lesions except for lymph nodes; short axis ≥ 15 mm for lymph nodes</td>
</tr>
<tr>
<td>Target lesion</td>
<td>All measurable lesions up to two per organ and five in total, selected on baseline scan; all other lesions or sites are recorded as nontarget lesions</td>
</tr>
<tr>
<td>Response Category</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>Disappearance of all target and nontarget lesions except for lymph nodes; all lymph nodes must be &lt; 10 mm short axis</td>
</tr>
<tr>
<td>Partial response</td>
<td>≥ 30% decrease in the sum of the longest diameters of target lesions compared with baseline</td>
</tr>
<tr>
<td>Stable disease</td>
<td>Neither partial response or progressive disease</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>≥ 20% and ≥ 5-mm increase in the sum of the target lesion measurements compared with the smallest sum recorded; the appearance of one or more new lesions; or unequivocal progression of nontarget lesions</td>
</tr>
</tbody>
</table>

**PRACTICAL APPLICATIONS**

- RECIST1.1 is the current version of tumor response criteria that are widely accepted as a standardized method in most trials of solid tumors in general; it uses unidimensional diameters of target lesions and the sum of measurements of all target lesions as a quantitative measure of tumor burden.
- Major limitations of RECIST that universally affect the response assessment regardless of tumor types or agents include variability of tumor size measurements and tumoral heterogeneity both within a lesion and among different lesions in a patient.
- Among the specific limitations of RECIST in precision cancer therapy, in patients treated with molecular targeting agents with antiangiogenic activity, decrease of CT tumor density may reflect response to therapy even without tumor size decrease meeting the criteria for RECIST response; Choi criteria can contribute to address the pitfall.
- In patients with tumors harboring specific genomic abnormalities treated with effective molecular targeting therapy, tumors tend to show marked initial response and then slowly grow back while the patients are receiving therapy, where RECIST progression does not necessarily indicate treatment failure and the tumor growth rate may contribute to help therapeutic decisions.
- In patients treated with cancer immunotherapy using immune-checkpoint blockade, atypical response patterns or pseudoprogression, although rare, can be noted, and several criteria have been proposed to address the unmet needs in the emerging field.

Abbreviation: RECIST, Response Evaluation Criteria in Solid Tumors.

*Longest diameter of ≥ 0 mm on nonhelical CT with a slice thickness of > 10 mm or on chest radiography.
TUMOR RESPONSE ASSESSMENT FOR PRECISION CANCER THERAPY

Tumor volume is more reproducible than size, indicating an additional advantage of using tumor volume for accurate characterization of tumor response to therapy.8,14-19 Tumor volume has also been shown to be a useful early marker to predict survival in a subset of patients with advanced cancer treated with molecular targeted therapy.16,17 It has been almost a decade since the RECIST Working Group, at the time of introduction of RECIST 1.1 in 2009, addressed moving from unidimensional assessment to volumetric or functional assessment, but it concluded that sufficient standardization and widespread availability were needed before the alternative methods could be recommended.4,6 Robust solutions for the increasing needs for standardization and technology transfer should be established via collaborations among oncology and radiology communities.

FIGURE 1. 55-Year-Old Woman With Non–Small Cell Lung Cancer Treated With EGFR Inhibitor Erlotinib

(A) CT scan of chest shows spiculated right lung lesion, which was only target lesion, has longest diameter of 2.8 cm (arrow). (B) After one cycle of therapy, lesion measures 1.3 cm (arrow), showing 54% decrease in size compared with baseline. This change is consistent with partial response. (C) After initial response, small residual tumor slowly increased in size and measured 1.7 cm (arrow) on further follow-up study. Given 30% increase compared with nadir (1.3 cm), assessment by using the original Response Evaluation Criteria in Solid Tumors (RECIST 1.0) would be progressive disease (PD). However, by using RECIST 1.1, assessment is stable disease because absolute increase in size is less than 5 mm. (D) Another follow-up CT scan shows further increase in size of residual tumor with longest diameter of 2.0 cm (arrow), which meets criteria for PD by RECIST 1.1 given 54% increase and 6-mm absolute increase in size compared with nadir.


SPECIFIC LIMITATIONS IN THE SETTING OF PRECISION CANCER THERAPY

Along with the further advancement of the precision medicine approaches for the care of patients with cancer,
additional limitations of RECIST that are relevant in the specific setting of precision cancer treatment have been increasingly recognized. To represent these emerging limitations of RECIST, three clinical scenarios are presented: (1) CT density changes in response to molecular targeted therapy, (2) slow tumor progression during molecular targeted therapy, and (3) response evaluations in cancer immunotherapy.

CT Density Changes in Response to Molecular Targeted Therapy
In patients treated with molecular targeting agents especially with antiangiogenic activity, decrease of CT tumor density may reflect response to therapy (Fig. 4), even in the absence of tumor size decrease of 30% or more as defined by RECIST.2,20-22 CT density is measured on the CT images by placing a region of interest (ROI) over a lesion or an area, and is demonstrated using the Hounsfield unit (HU) value, where water is 0 HU and air is −1,000 HU. CT density measurement is a relatively simple and practical procedure that is routinely performed in the interpretation of CT scans, however, is subject to measurement variability. The phenomenon of CT density decrease as a manifestation of tumor response to therapy has been most studied in gastrointestinal stromal tumors treated with tyrosine kinase inhibitors; however,
similar observations are noted in other solid tumors, including other sarcomas, renal cell carcinomas, and hepatocellular carcinomas.\textsuperscript{2,23-25} After initial response to therapy with CT density decrease, tumor progression may demonstrate such patterns as an appearance of new intratumoral nodules or new enhancement, rather than tumor size increase (Fig. 4).\textsuperscript{2,20-22,26} To complement the limitations of RECIST in this setting, Choi response criteria have been proposed, which define response by a 10% decrease in tumor size or a 15% decrease in CT density. Choi criteria also define progression by (1) appearance of new lesions, (2) appearance or increase in size of intratumoral nodules, or (3) tumor size increase by more than 20% without post-treatment hypodense change.\textsuperscript{20,21} The Choi criteria are widely recognized and often used as a secondary guideline to evaluate tumor response and progression in the specific settings of antiangiogenic activity.

**Slow Tumor Progression During Molecular Targeted Therapy**

Recent advances of tumor genomic analysis have enabled precision oncology approaches using molecular targeting agents for patients harboring specific genomic abnormalities in their tumors. Tumors of these patients show marked initial decrease in response to therapy but subsequently demonstrate regrowth because of acquired resistance, as represented by patients with advanced NSCLC who have sensitizing \textit{EGFR} mutations treated with \textit{EGFR} inhibitors.\textsuperscript{2,5,27,28} In these patients, tumors tend to grow back slowly over the course of many months or sometimes a few years after reaching the nadir.\textsuperscript{16,17,29} Oncologists often continue to treat these patients with \textit{EGFR} inhibitors even after they met the criteria for RECIST progression because their tumors continue to grow slowly, suggesting that some tumor cells remain sensitive to \textit{EGFR} inhibitors.\textsuperscript{20,21} In a report of 56 patients with \textit{EGFR}-mutant NSCLC treated with \textit{EGFR} inhibitors, 88% of the patients continued \textit{EGFR} inhibitors after they met the criteria for RECIST progression (Fig. 5).\textsuperscript{32} A recent phase II trial of \textit{EGFR}-mutant patients treated with first-line \textit{EGFR} inhibitor showed that continuation of therapy beyond RECIST progression is feasible and delayed salvage therapy by a median of 3.1 months.\textsuperscript{33} Similar clinical scenarios are noted in other tumors, including patients with \textit{ALK}-rearranged NSCLC treated with anaplastic lymphoma kinase inhibitors.\textsuperscript{2,34-38} The limited value of RECIST in these settings is somewhat expected because RECIST was primarily designed to document tumor response to therapy in trials and was not intended to guide treatment decisions.\textsuperscript{3,4,39} Regardless, increasing clinical demands should be recognized to support the efforts to objectively characterize slow progression over time and distinguishing patients who can safely continue receiving therapy from those who need alternate therapy.

**FIGURE 5. 50-Year-Old Woman With Lung Adenocarcinoma Harboring Sensitizing \textit{EGFR} Mutation (Exon 19 Deletion)**

(A) Baseline chest CT before therapy demonstrated an irregular mass in the left upper lobe, measuring 3.1 cm. (B) The patient started treatment with erlotinib and demonstrated marked tumor decrease as a response to therapy. After 11 months of therapy, the left upper lobe lesion measured 0.8 cm (arrow), which was the smallest measurement since the baseline. (C) The lesion started to grow slowly. At 15 months of therapy, the lesion measured 1.4 cm (arrow), meeting the criteria for progression by Response Evaluation Criteria in Solid Tumors 1.1 (≥20% and ≥5-mm increase since the nadir). Given the small burden of the tumor, the patient continued to receive erlotinib without any additional agent. (D and E) At 22 months of therapy, the left upper lobe lesion further increased in size, measuring 4.1 cm (arrow). MRI of the cervical spine demonstrated diffuse leptomeningeal enhancement (arrowheads), representing new leptomeningeal metastasis. Erlotinib was discontinued, and the patient was subsequently enrolled in another investigational therapy.
To address slow progression, some investigators have focused on tumor growth rate during therapy as a marker for defining treatment endpoints and assessing clinical benefits. In the studies by Stein and colleagues in cohorts with renal cell carcinoma and prostate cancer, the tumor growth rate constant, obtained as loge2/doubling time (days) using tumor size measurements during trials, showed negative correlation with overall survival, demonstrating that slow tumor growth indicates better outcome. In patients with advanced EGFR-mutant NSCLC treated with EGFR inhibitors, the tumor growth rate after nadir was 0.12 per month for the logarithm of the volume (logV), which was reproduced in an independent cohort, proposing a reference value to define slow progression in this specific population to better guide therapeutic decisions (Fig. 6). Further efforts are ongoing to validate these findings and translate the approach into the clinical setting.

FIGURE 6. CT Images of Segmented Lung Tumor From 52-Year-Old Woman With Stage IV Lung Adenocarcinoma With Slow Tumor Growth

(A) Baseline CT scan revealed a dominant right upper lobe lesion measuring 14,495 mm³. (B) The patient received treatment with gefitinib, and her tumor volume significantly decreased, reaching the nadir, measuring 4121 mm³, at 8 months. (C-H) The tumor started to grow back, with a gradual increase in tumor volume over 2 years observed after (C) 11 months, (D) 16 months, (E) 19 months, (F) 21 months, (G) 26 months, and (H) 28 months of therapy. The maximum tumor growth rate (measured by using the logarithm of tumor volume [logV]) between two consecutive scans since nadir was 0.09 mm³ per month. Gefitinib was discontinued at 28 months, and the patient subsequently was treated in a trial with an irreversible EGFR inhibitor.


FIGURE 7. Response After an Initial Increase in Total Tumor Burden in 77-Year-Old Man With Advanced Melanoma Treated With Ipilimumab

(A) Baseline CT scan demonstrated a lung lesion (arrow) measuring 19 mm in the longest diameter. (B) At 12 weeks of therapy, the lesion (arrow) measured 29 mm, demonstrating 53% increase compared with baseline, indicating progressive disease by Response Evaluation Criteria in Solid Tumors (RECIST). (C) The patient continued to receive therapy, and another follow-up CT scan at 24 weeks showed a reduction of the lesion (arrow), measuring 12 mm, indicating immune-related response to therapy.

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TUMOR RESPONSE ASSESSMENT FOR PRECISION CANCER THERAPY

Cancer immunotherapy using immune checkpoint inhibitors have brought a paradigm shift in advanced cancer treatment in the past few years.45-48 Anticancer mechanism of immune checkpoint inhibitors is via blockade of immune inhibition by tumors.46-48 Because of this unique mechanism of action, atypical response patterns are noted in patients treated with immune checkpoint inhibitors, including response after an initial increase in tumor burden and response during or after appearance of new lesions (Figs. 7 and 8). These response patterns are termed "pseudoprogression" because the initial increase or appearance of new lesions meets the criteria for RECIST progression.2,46,49-51 To overcome limitations of RECIST and capture these additional response patterns during immunotherapy, several response criteria have been proposed specifically for patients treated with cancer immunotherapy and continue to evolve as we learn more about immune-related tumor responses (Table 2).

The first criteria for cancer immunotherapy were proposed in 2009 as immune-related response criteria (irRC).50 The key features of irRC include (1) requirement of confirmation of PD on two consecutive scans obtained at least 4 weeks apart and (2) inclusion of new lesion measurements in the entire tumor burden, rather than defining PD at the appearance of new lesions.50 Subsequently, the studies by Nishino and colleagues showed that RECIST-based unidimensional measurements, as opposed to bidimensional measurements used in irRC, can characterize immune-related tumor responses with better reproducibility, while keeping the important features of irRC in terms of progression.

### TABLE 2. Summary of Criteria for Immune-Related Response Evaluations

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurement</strong></td>
<td>Bidimensional</td>
<td>Unidimensional</td>
<td>Unidimensional</td>
</tr>
<tr>
<td>LD × SD (cm²)</td>
<td>LD (cm) for non–lymph node lesions</td>
<td>LD (cm) for non–lymph node lesions</td>
<td></td>
</tr>
<tr>
<td>SD (cm) for lymph nodes</td>
<td>SD (cm) for lymph nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PR Criteria</strong>*</td>
<td>≥ 50% decrease</td>
<td>≥ 30% decrease</td>
<td>≥ 30% decrease</td>
</tr>
<tr>
<td><strong>PD Criteria</strong></td>
<td>≥ 25% increase</td>
<td>≥ 20% and ≥ 5-mm increase, or nontarget PD</td>
<td>≥ 20% and ≥ 5-mm increase, or nontarget PD</td>
</tr>
<tr>
<td><strong>New Lesions</strong></td>
<td>Included in the sum of measurements</td>
<td>Included in the sum of measurements</td>
<td>Recorded and measured separately and not included in the sum of measurements</td>
</tr>
<tr>
<td><strong>Confirmation of PD</strong></td>
<td>Required</td>
<td>Required</td>
<td>Required</td>
</tr>
<tr>
<td></td>
<td>At least 4 weeks later</td>
<td>At least 4 weeks later</td>
<td>At the next assessment performed 4-8 weeks later</td>
</tr>
</tbody>
</table>

Abbreviations: iRECIST, Response Evaluation Criteria in Solid Tumors for immunotherapy; irRC, immune-related response criteria; irRECIST, immune-related Response Evaluation Criteria in Solid Tumors; LD, longest diameter; PD, progressive disease; PR, partial response; SD, short-axis diameter (longest perpendicular diameter). Data obtained from Nishino et al.46

*The percentage change is calculated in comparison with the measurements at baseline.

**The percentage change is calculated in comparison with the measurements at the nadir (smallest tumor burden since baseline).

†Defined as a ≥ 5 mm for sum of new lesion target or any increase in new lesion nontarget.

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### FIGURE 8. Pseudoprogression in 66-Year-Old Man With Advanced Melanoma Treated With Pembrolizumab

(A) Baseline CT scan showed no measurable tumor burden and subcentimeter, nonmeasurable brain metastasis. (B) A follow-up scan at 1.5 months of therapy showed a new subcutaneous nodule (arrow). (C) On a subsequent follow-up scan at 3.5 months of therapy, the nodule has significantly decreased in size (arrow). Reprinted with permission from Clin Cancer Res. 2017;23:4671-4679.
confirmation and new lesion assessment.\textsuperscript{32,53} The studies provided a basis for RECIST-based immune-related response evaluations, which became known as immune-related RECIST among the investigators of immuno-oncology (Table 2).\textsuperscript{46,47}

More recently, RECIST working group developed iRECIST that is specifically designed for cancer immunotherapy trials.\textsuperscript{55} iRECIST is also based on unidimensional RECIST-based approach and requires confirmation for PD, while it proposed separate assessments for new lesions and defined an important concept of unconfirmed PD (Table 2).\textsuperscript{55} These efforts have contributed substantially to develop a common language to assess response to immunotherapy.\textsuperscript{46}

Because the concepts and guidelines for cancer immunotherapy are evolving, the cutting-edge observations from the recent studies of immune-related response assessments can provide substantial contributions to this emerging field. An important recent observation is the low incidence of pseudoprogression, which should be recognized by providers who evaluate patients treated with cancer immunotherapy.\textsuperscript{46,51,56} Among patients with melanoma treated with immune checkpoint inhibitors, the incidence of pseudoprogression is approximately 10% or lower.\textsuperscript{49,50,57,58} Among patients with advanced NSCLC, a lower incidence of 5% (6 of 129) was reported in a phase I study of nivolumab.\textsuperscript{59} The incidence seems even lower in patients with NSCLC treated with standard-of-care PD-1 therapy; in a recent study of 160 patients treated with commercial nivolumab or pembrolizumab monotherapy, only one patient (0.6%) demonstrated pseudoprogression, emphasizing the rarity of the phenomenon.\textsuperscript{60} Additionally, the detailed analyses of the few pseudoprogression cases have indicated another limitation of the current methods of immune-related response evaluations. In two recent studies of advanced melanoma and NSCLC treated with PD-1 inhibitors, patients with pseudoprogression showed tumor burden decrease after PD was confirmed on two consecutive scans, suggesting that immune-related tumor response may occur much later than the currently assumed timeframe (4–8 weeks) after the initial PD (Fig. 9).\textsuperscript{58,60} These accumulating data provide insights for further improvement of the design of response criteria for immunotherapy and also indicate the area of unmet needs where more novel imaging techniques may be required.

Although the basic strategy of tumor response assessment is to simply obtain a proportional tumor burden changes (percentage) comparing to the reference scan (the baseline or the nadir scan), the longitudinal analyses of serial changes in tumor burden over time during therapy may more accurately reflect tumor behaviors in response to therapy. Such an approach may be particularly useful in the setting of cancer immunotherapy, where tumors demonstrate complex behavior reflecting the interplay of tumor biology, anticancer agent activity, and host immunity. In recent studies of serial tumor burden dynamics in patients treated with PD-1 inhibitors, a tumor burden increase of less than 20% in reference to the baseline burden throughout therapy was associated with longer survival, proposing a practical marker of treatment benefit.\textsuperscript{58,60} By applying the concept of tumor growth rate to immunotherapy, another recent report described a pattern of “hyperprogressive disease,” which demonstrates RECIST progression at the first evaluation with a twofold or greater increase in the tumor growth rate between the prior therapy period and upon anti-PD-1/PD-L1

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure9}
\caption{38-Year-Old Woman With Advanced Melanoma With Pseudoprogression}
\end{figure}

(A) Baseline CT scan showed a right axillary lymph node measuring 1.7 cm in short axis (arrow). The lesion increased in size on the first follow-up scan at 2.7 months (B) and second follow-up scan at 4.1 months (C), demonstrating increase in size of the lesion more than 20% from baseline, confirming immune-related progressive disease. The lesion reached its maximal size at the third follow-up scan at 5.5 months (D) and then started to decrease in size on the fourth scan at 6.7 months (E). The lesion further decreased in size gradually and met the criteria for response at 22.3 months of therapy (F). Since then, the lesion remained small and maintained durable response over 19 months. Reprinted with permission from Clin Cancer Res. 2017;23:4671-4679.
therapy. These emerging study results are provocative and suggest an increasing need for further investigations to optimize treatment monitoring for cancer immunotherapy, where the oncology and radiology community can work together to advance the field.

CONCLUSION AND FUTURE DIRECTIONS

RECIST has been a simple and practical method for tumor response evaluations in the past decades and has provided a basis for the regulatory approvals of novel anticancer agents as the most widely accepted and standardized measure to objectively describe treatment results. Limitations of RECIST, both in general and in the specific settings of precision cancer therapy, should be recognized to address the pitfalls and apply alternate methods to overcome these limitations. Among the recent advances in novel therapeutic approaches, cancer immunotherapy provides many emerging challenges in tumor response evaluations, and further efforts through multidisciplinary collaborations are needed to improve the strategy for immune-related response evaluations. Understanding RECIST and its limitations in the current setting of precision cancer therapy is essential to set a stage for further progress of the field toward applying functional and molecular imaging for tumor response evaluations.

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