Reply to Y. Inagaki et al

We thank Inagaki et al1 for their interest in our study published in *Journal of Clinical Oncology* on the safety of immune checkpoint inhibitors (ICIs) in patients with underlying inflammatory bowel disease (IBD).2 We found that the risk of ICI-related GI adverse events was higher in patients with underlying IBD than in patients without IBD (41% v 11%; P < .001). Inagaki et al raised concerns about considering diarrhea as the main symptom of GI adverse events, because diarrhea is a nonspecific symptom that can be explained by a variety of etiologies, such as infections or adverse effects of medications, especially in elderly patients and in patients receiving immunosuppressive therapy. In our study, however, diarrhea was considered related to ICI therapy only after exclusion of other causes of diarrhea, as recommended by the current treatment guidelines for ICI-related adverse events.3,5

We agree with Inagaki et al1 that it is challenging to differentiate between IBD flare and ICI-related enterocolitis, given their considerable clinical, endoscopic, and histopathologic resemblance, and therefore we did not attempt to distinguish between them.6 The exclusion of alternative etiologies of diarrhea such as infection through the use of stool panels, and confirmation where possible of endoscopic inflammation, reflects real-world practice in the diagnosis and management of both IBD flares and ICI-related enterocolitis. In our study, most patients who had ICI-related GI events underwent endoscopic evaluation (32 of 42). Among them, 84% had active histologic inflammation consistent with inflammatory colitis, and 10% (four patients) developed colonic perforation, consistent with IBD-like disease. The subset of patients with normal histology who were treated presumptively for ICI-related diarrhea were still included in our study, because the distribution of enterocolitis can affect the yield of endoscopic evaluation, and there are cases of ICI-induced diarrhea that may have normal endoscopic and histologic presentation.7 In addition, the response of GI adverse events to immunosuppressive therapy further supports these events as inflammatory GI toxicities of ICI therapy.

Furthermore, the flares seen in our cohort are unlikely to represent the natural history of IBD alone in these patients. Most of the IBD cohort (84%) was symptom free at the time they started ICI therapy, with the majority not receiving an immunosuppressive therapy within 3 months. The median time from last IBD flare to ICI initiation was 5 years. Among the GI toxicities considered in our study, the onset after a median of 62 days is consistent with the expected time course of ICI-related enterocolitis,8 and the 41% rate of short-term toxicity is inconsistent with the expected rate of spontaneous IBD flares. Of note, ICI-related GI events frequently coincide with GI infections,9 and thus by excluding patients with GI adverse events in the setting of positive infectious testing, we may have underreported the true rate of ICI-related GI toxicity.

Diarrhea is the most commonly reported symptom of ICI-related GI adverse events in published clinical trials,9 yet 88% of our cohort had colitis grading based on signs and symptoms of colitis. A key factor in delineating the cause of diarrhea is a careful assessment of the time elapsed between diarrhea and the initiating event. However, clinical judgment is sometimes needed to determine the most likely diagnosis, especially without set criteria or timelines for considering diarrhea related to a certain factor. The median time from initiation of ICI therapy to GI adverse events was 9 weeks, which is in concordance with published data.10

Inagaki et al1 cited a study by Geukens Foppen et al11 that reported a lack of correlation between diarrhea grade, endoscopic presentation, and treatment approach of ICI-related GI events. Thus, developing management plans based on clinical symptoms alone might not be the most appropriate approach, and further assessment of severity by endoscopy and histology may provide more reliable information that correlates with disease outcomes.7,12 Nonetheless, contemporaneous treatment guidelines for ICI-related adverse events still provide recommendations based on the Common Terminology Criteria for Adverse Events grade of diarrhea and colitis, and endoscopic assessment of ICI-related enterocolitis is not universal.3,5

In conclusion, we agree with Inagaki et al1 that diarrhea in patients receiving ICI therapy can be related to multiple causes and that thorough evaluation, ideally with endoscopy and biopsy, is needed to confirm the diagnosis of ICI-related GI events and exclude other etiologies. We believe that our study provides the best reflection of available clinical practice data and is important for guiding decision making in the treatment of patients with underlying IBD. Prospective clinical trials are merited to investigate the safety of ICI therapy in patients with underlying autoimmune diseases and are currently underway (ClinicalTrials.gov identifier: NCT03816345).
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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REFERENCES


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