In Reply We appreciate the detailed comments on our analysis of the association of radiation therapy (RT) with risk of adverse events (AEs) in patients receiving immunotherapy by Nopsopon et al. In response, we emphasize that our analyses are descriptive and that no causal interpretation is intended. This overarching fact addresses many of the critiques of the article. For example, the authors suggest presenting measures of association, eg, rate ratio, and providing confidence intervals for incidence rates of AEs. However, as results are descriptive, we provided proportions of AEs in each group so the reader can assess difference and ratios. The US Food and Drug Administration approaches analyses of AE data from clinical trials descriptively because these trials are not typically powered for AE analysis. To make inferential claims regarding AE-related outcomes, trials would need to be powered and designed as such, and the trials included in this analysis were not. Additionally, the authors contend that different methods, such as an outcome-specific model, could have been used for the analysis. While other methods may indeed be used, our study was exploratory and hypothesis generating, and we contend that our presented analyses are sufficient for those purposes.

When companies submit data to the US Food and Drug Administration for regulatory review, they also submit individual case report forms and detailed patient-level listings, including demographic and disease characteristics and treatment details. Therefore, we did have individual patient-level data and used these for our aggregated analyses. In terms of handling of missing data, after excluding patients for other reasons, we had only 371 (of 17,206) patients with missing data, as shown in the CONSORT diagram. Those patients were excluded from the analysis. We do not expect this exclusion of only a small fraction of a relatively large total patient population to meaningfully bias the results over the adjustments using statistical methods that are reliant on validity of several modeling assumptions. We agree with the authors that appropriate handling of missing data will be important for any confirmatory studies based on exploratory findings in this study, particularly when missing data are substantial.

Regarding the time range of this pooled analysis spanning years, we contend that as optimal therapeutic modalities and dosages for RT delivery have improved, the AE profile should improve as well. Thus, inclusion of data from an earlier time period would actually be more likely to show any inherent dangers of RT plus immunotherapy. The fact that this was not demonstrated to any great extent even when older techniques were included is more likely a reassuring than a confounding factor.

The rationale for pooling patients of heterogeneous oncological categories was to optimize patient numbers. The finding of a slightly lower skin AE rate in those who received RT vs those who did not may be due to chance alone but provides reassurance to our overall conclusion that RT does not appear to be associated with increased risk of serious AEs in patients receiving immunotherapy. Our overall exploratory and hypothesis-generating research may help clinicians in the design of future trials testing combinations of immunotherapy and RT.

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Published Online: May 5, 2022. doi:10.1001/jamaoncol.2022.0880
Conflict of Interest Disclosures: None reported.


CORRECTION

Errors in Byline: In the Brief Report entitled “Use of Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Initial Results From the Pembrozilumab Arm of a Phase 2 Randomized Clinical Trial,” published online July 1, 2021, and also in the August 2021 print issue of JAMA Oncology,1 Katherine M. Moxley, MD, was erroneously included in the byline, and Sagila George, MD, was mistakenly excluded. This article has been corrected online, and the Author Contributions section has been amended accordingly.1


Errors in Byline and Affiliations: In the Brief Report entitled “Evaluation of the Durability of the Immune Humoral Response to COVID-19 Vaccines in Patients With Cancer Undergoing Treatment or Who Received a Stem Cell Transplant,”1 there were errors in the 23rd author’s name and affiliation. “Ghosh Arnab” should be “Arnab Ghosh.” His affiliation was “Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City” but should be “Department of Zoology, Rajiv Gandhi University, Arunachal Pradesh, India.” This article was corrected online.