In Reply

We thank Drs Sun and Wei for their comments in response to our analysis of the monarchE randomized clinical trial assessing the efficacy of abemaciclib plus endocrine therapy (ET) compared with ET alone in patients receiving neoadjuvant chemotherapy.1 The authors acknowledge that the different metrics used in conveying clinical trial outcomes have their own values and limitations. Hazard ratio (HR), together with the P value from log-rank tests, is the standardized way of assessing treatment effect for time-to-event end points in the clinical trial setting. This is commonly accepted by regulatory agencies and medical communities around the world in interpreting treatment effect size in cancer trials, which drove the statistical design for key efficacy end points in the monarchE study.

To address the validity of the reported monarchE statistical analyses, the HR, which is the ratio of the hazard rates between treatment arms, provides a single-value summary of the effect size in the entire follow-up period. In the article, we interpret HR as a relative measure of instantaneous risk between treatment arms.1 Among the patients who received neoadjuvant chemotherapy in the monarchE trial, the invasive disease-free survival (IDFS) HR estimate of 0.61 reflects that the abemaciclib plus ET treatment reduced the instantaneous risk of developing an IDFS event by 39% compared with ET alone.

Additionally, while the 2-year IDFS rate is indeed limited to a selected time point, it does use the event occurrence information prior to 2 years, as it represents the likelihood of patients surviving without developing invasive disease up to 2 years.1 The 2-year landmark was chosen based on the duration of follow-up at the time of analysis, but the yearly IDFS rate will continue to be estimated for 3 years, 4 years, and beyond with longer follow-up to describe the evolution of effect size.

We appreciate the recommendation of using restricted mean survival time (RMST) to support the benefit of adjuvant abemaciclib in combination with ET. Similar to the yearly rate estimates, the time scope of the RMST measure is dependent on the selected time horizon of the follow-up period. Additionally, the RMST difference is also considered as an absolute measure of the difference, which poses challenges in interpretation in itself.2 It could be difficult to compare across trials, thus limiting the applicability in interpreting treatment benefit in the context of the current treatment landscape for the corresponding disease setting.

In summary, the primary efficacy analysis was assessed by HRs and log-rank tests as a standardized method in oncology clinical trials, together with a supplementary metric of absolute risk difference at specific time points.3–5 Those analyses had been prespecified in the statistical analysis plan when the study was designed.

As the purpose of this study1 is to present the treatment benefit of abemaciclib plus ET among patients who have received neoadjuvant chemotherapy, it would be the most clinically relevant and interpretable for physicians and patients to report the metrics that are aligned with the most extensively used measures as well as the prespecified analysis method in the study and the results included in the product label for the indicated population.

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Published Online: September 29, 2022. doi:10.1001/jamaoncol.2022.4531

Conflict of Interest Disclosures: Dr Martin reported personal fees from Lilly during the conduct of the study; grants and personal fees from Roche and Puma, grants from Novartis, and personal fees from AstraZeneca, Daiichi Sankyo, Lilly, Pfizer, Seagen, Taiho, Pierre Fabre, and Amgen outside the submitted work. Dr Johnston reported personal fees from Eli Lilly during the conduct of the study; personal fees from AstraZeneca, Novartis, Sanofi Genzyme, and Pfizer outside the submitted work. No other disclosures were reported.


CORRECTION

Error in Figure Axis Label: In the Original Investigation titled “Association of High Tumor Mutation Burden in Non–Small Cell Lung Cancers With Increased Immune Infiltration and Improved Clinical Outcomes of PD-L1 Blockade Across PD-L1 Expression Levels,”9 the y-axis label in Figure 1C was incorrect. It should have read “Overall survival, %.” The article has been corrected online.