Plasma Tumor Mutation Burden and Response to Pembrolizumab—Response

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We thank Xue and colleagues for their interest and insight into the findings from our recent article. To summarize, in an earlier analysis, we reported that patients with metastatic non–small cell lung cancer, with plasma tumor mutational burden (pTMB) ≥16 mutations per megabase (mut/Mb), had improved progression-free survival (PFS) after first-line standard-of-care pembrolizumab-based therapy. In an exploratory analysis, we reported that *STK11/KEAP1/PTEN* and *ERBB2* mutations may help identify pTMB-high patients unlikely to respond to first-line pembrolizumab-based therapy (1). Xue and colleagues evaluated gene mutation data for a total of 853 patients from the POPLAR and OAK trials, of which 19.2% of patients carried the *STK11/KEAP1/PTEN* mutations. In this non-prespecified analysis, they reported a numerically higher overall survival (OS) for patients with *STK11/KEAP/PTEN* wild-type genotype when treated with atezolizumab (median OS, 14.5 months). In addition, they reported that patients without *STK11/KEAP1/PTEN* mutations derived an OS benefit with atezolizumab regardless of the low allele frequency adjusted blood-based TMB (LAF-bTMB) levels. However, when these results were evaluated, there appeared to be a consistent trend toward numerically lower survival outcomes in those patients with a mutation, median OS of 7.3 months for atezolizumab overall. When this small population was further split into TMB groups, median OS of 15.9 and 5.7 months were reported for the LAF-bTMB–high and LAF-bTMB–low subsets, respectively, albeit with a lower TMB cutoff of 12 mut/Mb.

These analyses, while interesting, are purely exploratory, and must not be considered definitive. We would like to point out a few key differences. First, these data from the POPLAR and OAK trials evaluated the role of atezolizumab in the second-line setting, compared with our study that was limited to pembrolizumab-based therapy in the first-line setting. Second, in our study, we demonstrated that combining loss-of-function mutations in *STK11/KEAP1/PTEN* and activating ERBB2 exon 20 insertion mutations with pTMB improved the ability to predict response. Inclusion of RECIST response data, and PFS from the POPLAR and OAK trials would be meaningful to discern an association between these mutational signatures, TMB, and response. Finally, as we develop novel methods of calculation of plasma TMB, questions emerge about the standardization of these values across different panel sizes, variant type inclusion, and determination of appropriate cut-off points. Our analysis used a 2.145-Mb next-generation sequencing panel, and analyzed pTMB as a continuous variable. Whether our results can be replicated on another panel, using LAF-bTMB score, that used a lower cutoff is an open research question.

The divergent data presented here on the role of *STK11/KEAP1/PTEN* mutations (2) and their interplay with outcomes following immunotherapy alone or in combinations can be potentially explained by the complex molecular interactions that exist within the tumor microenvironment, and argue for larger scale validation of pTMB. As noninvasive assays for TMB assessment become increasingly utilized in the clinic, there is an urgent need for harmonization of key aspects of panel-based TMB estimation, reporting, and analytic validation. We appreciate the interest of Xue and colleagues in the research findings, and acknowledge that many of their critiques have been addressed in our article.

Authors' Disclosures

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