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Plasma Tumor Mutation Burden and Response to Pembrolizumab-Response

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We have carefully reviewed the letter from Li et al and believe that there were misunderstandings of the results and interpretation of the findings, which we would like to take the opportunity to clarify.

We agree with Li et al that a prognostic biomarker provides information about the patient's overall cancer outcome, regardless of therapy, whilst a predictive biomarker gives information about the effect of a therapeutic intervention. As we discuss in the paper, mutations in *STK11/KEAP1* have been associated with inferior outcomes in patients treated with pembrolizumab-based chemotherapy, including among patients with high tissue TMB and PD-L1–positivity, suggesting a predictive role[1]. Additionally, we acknowledge that the biomarkers that have been studied are both predictive and prognostic. The results from the MYSTIC trial confirmed the negative prognostic role of *KEAP1* using plasma NGS in patients with metastatic NSCLC receiving combination immunotherapy; however, it did not clearly confirm the predictive role for *STK11*, but rather showed that this may be a prognostic biomarker, with overall worse outcomes seen in patients with *STK11* mutation[2]. The authors provide an example of a study where *STK11* has been shown to be a prognostic biomarker, however, two factors must be considered when taking this study into consideration. Firstly, patients on this study were not treated with pembrolizumab-based therapy, and secondly, role of co-existing mutations, PD-L1 and TMB has not been reported. Therefore, no direct conclusions can be made. The divergent data on the role of *STK11/KEAP* mutations and their interplay with outcomes following immunotherapy-based combinations can be potentially explained by the complex molecular interactions that exist within the tumor microenvironment.

Regarding their second critique that in our study overall survival (OS) was insignificantly linked to plasma TMB, we would like to point out that previous studies cited by Li et al have also failed to show this correlation with OS and in fact, the results from our study are consistent. For example, on the B-F1RST study, median OS for blood TMB high vs. low was NE vs. 13.1 months; HR = 0.77 (90% CI, 0.41–1.43; P = 0.48)[3].

Finally, we would like to clarify that pTMB is currently a research only assay, and is not ready for primetime use to guide clinical practice. We recognize that our observations are

Disclosures

C. Aggarwal is an advisory board member/unpaid consultant for Bristol-Myers Squibb, Celgene, Eli Lilly, Merck, Roche, and AstraZeneca. J.C. Thompson is an advisory board member for Guardant Health. E. L. Carpenter disclosed no potential conflicts of interest.

based on small numbers and, as stated in our paper, these analyses should be considered exploratory. We raise an idea for evaluation of these findings in a larger, prospective trial, and if validated, could suggest that including these genomic biomarkers may improve identification of pTMB-high patients unlikely to respond from immunotherapy.

Acknowledgments

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