Letters

COMMENT & RESPONSE

In Reply We thank Fabrizio and colleagues for their comments on our Invited Commentary on the role of tumor mutational burden in selecting patients with lung cancer for first-line immunotherapy.1 The Checkmate 227 study was amended to add a co-primary end point of progression-free survival (PFS) by tissue TMB, with the TMB cutoff prespecified as 10 mutations per megabase (mut/Mb), based on data from the phase 2 CheckMate 568 study (NCT02659059).2 The relationship between plasma TMB and outcome in the MYSTIC study was an exploratory end point only, with the optimal blood TMB cutoff of 20 mut/Mb being retrospectively determined, rather than prospectively defined as in CheckMate 227.3,4 Both studies used the FoundationOne CDx assay for tumor TMB testing on archival/fresh tumor tissue collected prior to study enrollment, with valid TMB data available for only 57.7% and 41.1% of randomized patients from the CheckMate 227 and MYSTIC studies, respectively.

Fabrizio and colleagues cite the 87% success rate of tumor testing using the FoundationOne CDx assay in the SOL01 phase 3 study of maintenance olaparib following first-line platinum-based chemotherapy for BRCA-mutated ovarian cancer (NCT01844986). It is not surprising that in this study of patients with ovarian cancer, where surgical debulking was required for eligibility for the study, that tissue collection would yield more samples amenable to molecular testing. This remains a significant challenge for newly diagnosed metastatic non-small cell lung cancer, where the location and accessibility of the primary tumor and metastatic site often present a barrier to obtaining an optimal amount of tissue.

Tumor mutational burden testing has technical limitations, with variable gene panels to estimate TMB ranging from 324 to 607 genes, covering 0.8 to 1.72 Mb of genomic coding sequence, some panels including synonymous exonic variants in TMB estimation, and some panels overestimating TMB through use of tumor-only approaches with variant filtration based on population databases, rather than use of matched normal tissues.4 Plasma TMB testing in the MYSTIC study was assessed using the 500-gene Guardant OMNI next-generation sequencing platform. The optimal TMB cutoff of 20 mut/Mb differs from the phase 3 EAGLE study of durvalumab with or without tremelimumab vs standard chemotherapy in relapsed/refractory head and neck cancer, which defined a lower optimal TMB cutoff of 16 mut/Mb for improved overall survival with immunotherapy.5 Using the same assay, plasma TMB as a continuous variable was not significantly associated with survival in patients treated with pembrolizumab in combination with chemotherapy in the KEYNOTE-189 trial.6

Phase 1 of the Friends of Cancer Research TMB Harmonization Project,4 published after our commentary was submitted for publication, used The Cancer Genome Atlas data to identify theoretic variability in panel-derived TMB estimates from 11 academic and commercial laboratories, relative to standardized whole-exome sequencing-derived TMB and highlighted the variability in panel-based TMB estimation, with the least variability observed in cancers of the lung, head, and neck. Phase 2 of this project will analyze variations across these panels using clinical patient formalin-fixed paraffin-embedded samples, while phase 3 will establish optimal TMB cutoffs from samples obtained from patients treated with immunotherapy as part of a clinical trial.4 In the meantime, the clinically meaningful TMB cutoff remains mystic.

Sajana N. Waqar, MBBS, MSCI
Ramamowry Govindan, MD

Author Affiliations: Division of Oncology, Department of Medicine, Washington University School of Medicine in St Louis, St Louis, Missouri.

Corresponding Author: Ramamowry Govindan, MD, Division of Medical Oncology, Washington University School of Medicine, 660 S Euclid Ave, IDE Box 8086, St Louis, MO 63110 (rgovindan@wustl.edu).


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