Tumor Mutation Burden: Leading Immunotherapy to the Era of Precision Medicine?

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Non–small-cell lung cancer (NSCLC) exemplifies precision medicine, with multiple Food and Drug Administration–approved targeted therapies that are based on genomic biomarkers such as EGFR, ALK, ROS1, and BRAF. Recently, immunotherapy became accepted broadly as an effective treatment modality for patients with cancer. However, the ability to select patients who will benefit from immunotherapy remains limited. Tumor mutational burden (TMB) is promising as a predictive biomarker and potentially could lead the way for immuno-oncology to enter the era of precision medicine.

The targeting of the inhibitory programmed death-ligand 1 (PD-L1)/programmed death-1 (PD-1) axis with immune checkpoint blockade has proven to be an effective immuno-oncology strategy. In metastatic NSCLC, checkpoint inhibitors were first approved in the second-line setting. Nivolumab (hazard ratio [HR], 0.72), pembrolizumab (HR, 0.71), and atezolizumab (HR, 0.73) all demonstrate improved survival over docetaxel in patients who experience treatment failure with platinum doublet therapy.1–3 Recently, pembrolizumab was approved for first-line therapy in patients with NSCLC whose tumors have ≥ 50% PD-L1 expression, with an impressive 30.2-month median overall survival (OS) compared with 14.2 months for chemotherapy.4

In melanoma, Snyder et al8 noted that TMB by whole-exome sequencing (WES) is a predictor of increased survival for patients who receive ipilimumab or tremelimumab. Tumors with higher TMB have been hypothesized to have more neoantigens that can be recognized by the immune system in response to checkpoint inhibition. In a separate study, WES was performed in 34 patients with NSCLC who received pembrolizumab, and improved overall response rates (ORRs), progression-free survival (PFS), and durable clinical benefit in patients with high somatic nonsynonymous mutation burden were observed.9 Recently, TMB was examined as part of an exploratory analysis of the Checkmate 026 study, which compared nivolumab with platinum doublet chemotherapy in first-line metastatic NSCLC. For patients with a high TMB, the response rate was higher in those who received nivolumab versus chemotherapy (47% vs. 28%), and PFS was improved (9.7 vs. 5.8 months). Of note, patients with high TMB and high PD-L1 had the best outcomes, and those who were negative for both did the worst.10 In all these

Key points

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NSCLC, use of these drugs in the clinic remains imprecise, with a limited ability to identify patients who will benefit from treatment. PD-L1 expression is the only predictive biomarker currently used for patient selection, but it is an imperfect biomarker with several limitations.5–7 Therefore, the development of biomarkers, such as TMB, to aid patient selection continues to be a major focus of ongoing research efforts.
An important aspect of the study reported by Rizvi et al is the correlation between TMB determined by NGS versus WES in an admittedly small cohort of 49 patient samples (Spearman $\rho = 0.86$; $P < .001$). Each of these studies, however, defined high TMB at various thresholds and used different NGS panels. The molecular testing platforms currently in use also have a wide degree of variance in the gene panels used; hence, the harmonization of TMB across these platforms and the definition of the optimal threshold to define the high group that can be used for treatment selection are necessary next steps for the field. Prospective evaluation of TMB as a biomarker to select treatment with checkpoint inhibitors is already under way, and the results are eagerly awaited.

An important aspect of the study reported by Rizvi et al is the correlation between TMB determined by NGS versus WES in an admittedly small cohort of 49 patient samples (Spearman $\rho = 0.86$; $P < .001$). Even during the time the specimens were evaluated, the MSK-IMPACT platform underwent several iterations, which reflects the rapid changes in genomic testing technology in oncology. The study results are supported by observations from another study that noted a good correlation in clinical outcomes with checkpoint inhibition on the basis of TMB determination by NGS or WES. If TMB becomes a marker for use in routine clinical practice, it is more likely to be determined by NGS rather than by WES. From this standpoint, the data reported in these two studies assume great significance. Confirmation of these observations in the context of a larger clinical trial is an essential step before adoption of TMB by NGS as a predictive biomarker.

These lines of evidence clearly suggest that TMB could play a valuable role in treatment selection for immune checkpoint inhibition. However, the limiting factors include tissue specimen availability, wide genomic heterogeneity of tumors, varying testing platforms, the relatively longer turnaround time, access to state-of-the-art testing, and cost. Recently, assessment of TMB in cell-free DNA in peripheral blood was shown to be predictive of benefit from immune checkpoint inhibition. If confirmed, this
could improve the feasibility of assessment of TMB in many ways.

A number of other emerging biomarkers, such as tumor-infiltrating lymphocytes, specific immune gene signatures, T-cell receptor clonality, monitoring of peripheral blood T cells, and imaging biomarkers, hold promise in selecting patients for treatment with checkpoint inhibitors. As we make rapid strides in cancer care, we should not forget that not too long ago, tumor tissue only was used to determine histologic status. The studies by Rizvi et al and others provide evidence on how far we have come in a relatively short time and provide hope that current research will lead to a tailoring of cutting-edge treatments for patients to maximize clinical benefits cost-effectively.

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References