Editorial

Predictive biomarkers for immune checkpoint inhibitor therapy: we need to keep searching

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Immune checkpoint inhibitors are being increasingly used in the management of advanced non-small cell lung cancer (NSCLC). Identifying patients most likely to respond to these agents has become an increasingly important area of investigation. In a recently published analysis, Dr. Hellman and colleagues evaluated the characteristics of tumor mutational burden (TMB) as a biomarker for sensitivity to checkpoint inhibition (1). The aim of this study was to stratify patients on the basis of TMB—high or low—and evaluate whether TMB serves as a useful tool for selecting patients more likely to respond to first-line nivolumab plus ipilimumab compared to traditional chemotherapy.

Checkmate 227, an open-label, phase III trial was designed to evaluate the use of nivolumab (alone or in combination with ipilimumab) compared to cytotoxic chemotherapy as first line treatment for patients with advanced NSCLC. Studies identified TMB as a possible biomarker for likelihood of response to checkpoint inhibition, and the protocol was retrospectively amended to include the co-primary endpoint of progression free survival (PFS) in patients stratified by high or low TMB and treated with nivolumab plus ipilimumab or chemotherapy.

The study population included patients with recurrent or stage IV NSCLC who had not received systemic therapy and did not have targetable molecular abnormalities. Of 1,739 randomized patients, 1,004 ultimately had adequate tissue and valid analysis of TMB. Forty-four percent (444 patients) had >10 mutations per megabase. This number has been proposed to represent a clinically significant threshold in terms of predicting response to nivolumab plus ipilimumab in a variety of solid tumors. Patients in the chemotherapy arm received a platinum-based doublet every three weeks for up to four cycles (with the option of maintenance pemetrexed for those with non-squamous histology). Patients in the nivolumab plus ipilimumab arm received nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every six weeks continued until progression, discontinuation, or 2 years.

The 444 patients with high TMB included 139 who had received nivolumab plus ipilimumab and 160 who received chemotherapy. PD-L1 expression was balanced between treatment groups, and there was no correlation between PD-L1 expression and TMB. A higher proportion of patients in the chemotherapy group discontinued for disease progression, while discontinuation due to adverse events was more common in the immunotherapy group.

Among all randomized patients (regardless of PD-L1 expression or TMB) PFS was longer in patients who received nivolumab plus ipilimumab than those who received chemotherapy: 1-year PFS was 30.9% *vs.* 17.0%. The benefit of checkpoint inhibition was more pronounced for patients with >10 mutations per megabase (high TMB), with 1-year PFS in this population 42.6% for patients in the combination immunotherapy arm

and 13.2% in those receiving chemotherapy. This finding held true regardless of PD-L1 expression. The benefit of immunotherapy was not seen for patients with <10 mutations per megabase (low TMB). For patients with low TMB, PFS was 3.2 months in those receiving nivolumab plus ipilimumab and 5.5 months for those receiving chemotherapy, which did not represent a significant difference. A pertinent secondary endpoint included PFS in patients treated with nivolumab monotherapy *vs.* chemotherapy in patients with >13 mutations per megabase and PD-L1 >1%. Of the patients who met these criterions, 71 received nivolumab and 79 received chemotherapy. There was no difference in PFS between groups, with a median of 4.2 months for immunotherapy and 5.6 months for chemotherapy.

The characteristics of a clinically useful predictive biomarker include a non-invasive, cost effective and reproducible assay with exceptional specificity and sensitivity for identifying those who will and will not respond. When a biomarker is used for treatment planning, the stakes may be even higher than in biomarkers used for screening or response to therapy. In this paradigm, the consequence of a false positive or negative result may well be an inappropriate first line therapy and the associated morbidity in terms of lost length and quality of life.

Immunohistochemical quantification of PD-L1 expression in tumor cells has helped predict response to treatment with checkpoint inhibitors, primarily monoclonal antibodies against PD-1 (pembrolizumab, nivolumab) or PD-L1 (atezolizumab, durvalumab). Patients whose tumors express PD-L1 at high levels generally have a better response to immunotherapy. The Keynote-024 study demonstrated that for patients whose tumors had >50% cells expressing PD-L1, pembrolizumab had superior progression free (10.3 *vs.* 6 months) and overall survival [hazard ratio for death, 0.60 (95% CI, 0.41–0.89); P=0.005] as compared to chemotherapy (2).

PD-L1 expression does not always accurately predict which patients will or will not respond to checkpoint inhibition. For example, Keynote-010 evaluated pembrolizumab in previously treated patients with advanced NSCLC and found that in patients with high levels of PD-L1 expression (>50%), the use of checkpoint inhibition rather than docetaxel was associated with a significant improvement in response rate and overall survival (3). However, these data also show that 70% of patients with high PD-L1 expression will not have a response to PD-1 blockade. In contrast, in the Keynote 189 study, the addition of pembrolizumab to chemotherapy was associated with improved 12-month overall survival rate as compared to chemotherapy alone [69.2% *vs.* 49.4%; hazard ratio for death, 0.49 (95% CI, 0.38–0.64); P<0.001] (4). This improvement was seen in all subgroups regardless of PD-L1 expression. Interestingly, the addition of pembrolizumab was associated with an increased response rate even in patients without PD-L1 expression (32.3% *vs.* 14.3%; estimated treatment difference of 17.4%). These data demonstrate the need for a better predictive biomarker for benefit from checkpoint inhibition.

Ultimately, the primary drawback to the use of tumor PD-L1 expression as a predictive biomarker for response to immunotherapy is suboptimal positive and negative predictive value. The limitations of PD-L1 as a biomarker also include technical factors (multiple assays for PD-L1 staining developed on multiple platforms, inter-observer variability in quantification, non-binary results) and the biology of the biomarker itself (heterogeneity within a tumor, dynamic expression over time).

Checkpoint inhibitor therapy has been most effective in tumors associated with chronic mutagen exposure such as melanoma and lung cancer. These tumors sometimes have a high TMB, which leads to expression of a wide variety of neo-antigens. These non-native proteins are targets for a tumor-specific T cell response. Expression of PD-L1 is one mechanism by which malignancies escape immune surveillance. Checkpoint inhibition prevents escape and allows for robust T cell response against the tumor. This is the pathophysiologic backdrop for the study of TMB as a biomarker for response to immunotherapy (5).

TMB appears to provide an additional approach to choosing candidates most likely to respond to checkpoint inhibitor therapy. Rather than quantifying expression of a specific target, it may be a surrogate for the immunophenotypic "other"—ness of tumor surface antigens and therefore of the likelihood of response to therapies directed at enhancing the anti-tumor immune response.

From a technical standpoint, TMB assessment also has benefits and drawbacks. Genomic testing is not observer dependent. There are, however, a number of different multi-gene panels available, which assess varying assortments and numbers of genetic alterations. Additionally, the initial data for TMB used whole-exome sequencing—a technology not yet feasible in the clinical setting—and has varying degrees of correlation to the next generation sequencing assays used in clinical practice (6-10). The threshold for clinically significant TMB is also not well established, and one can imagine this cut point may vary based on the genomic panel in question.

This study also hints at our incomplete understanding

of TMB as a predictive biomarker. While it seemed to help delineate those who would and would not benefit from first-line, combined immunotherapy with PD-1 and CTLA-4 blockade, it did not predict response to single-agent nivolumab, even when combined with PD-L1 expression >1% and utilizing an increased threshold for "high" TMB (13 mutations per megabase). It is unclear why the authors chose to change the definition of high TMB for the nivolumab monotherapy arm, but we would expect a more stringent definition of high TMB to make it even more likely to predict a better response to nivolumab than chemotherapy. It remains to be seen whether this lack of difference is due to the constraints inherent to retrospective analysis of a small population or an indicator of our nascent understanding of biomarkers for predicting response to immunotherapy.

While the results of this study point towards the potential role of TMB as a predictive biomarker for response to immune checkpoint inhibition, a lot remains unclear at present. The current study did not describe the optimal method for testing for TMB. Will TMB testing provided by the current multiplex assays be equivalent to the results of whole exome sequencing? Will a combined TMB and PD-L1 expression be a better predictor marker than either assay alone? Further studies are needed to answer these questions satisfactorily.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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