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ABSTRACT

Immune checkpoint inhibitors, including antibodies that block programmed cell death protein-1 (PD-1) and PD-L1, have transformed the management of many cancers. However, the majority of patients have primary or acquired resistance to these immunotherapies. There is a significant unmet need for predictive biomarkers that can reliably identify patients who derive a clinically meaningful response from PD-1/PD-L1 blockade. High tumor mutational burden (TMB-H) has shown promise as a biomarker in lung cancer, but the broad applicability of TMB-H as a biomarker of response across all solid tumors is unclear. The FDA has approved the PD-1 inhibitor, pembrolizumab, as a therapy for all solid tumors with TMB equal to or greater than 10 mutations/megabase as measured by the FoundationOne CDx assay. This approval was based on an exploratory analysis of the KEYNOTE-158 study, which was a single-arm, phase II multicohort study of pembrolizumab for select, previously treated advanced solid tumors. Here, we elucidate the caveats of using TMB as a biomarker with a universal threshold across all solid tumors. While we recognize the importance of this and other FDA pan-cancer approvals, several questions about TMB as a predictive biomarker remain unanswered. In this perspective, we discuss clinical trial evidence in this area. We review the relationship between TMB and the tumor immune microenvironment. We highlight the risks of extrapolating evidence from a limited number of tumor histologies to all solid tumors, and we propose avenues for future research.

Introduction

On June 16, 2020, the FDA approved the programmed cell death protein-1 (PD-1) inhibitor, pembrolizumab (KEYTRUDA, Merck & Co., Inc.), for the treatment of tumor mutational burden–high (TMB-H) solid tumors. The FDA approved pembrolizumab on the basis of the KEYNOTE-158 study, which was a single-arm, phase II multicohort study of pembrolizumab for select, previously treated advanced solid tumors (1). In this study, 105 patients met the prespecified criteria for TMB-H (>10 mutations (muts)/megabase (Mb) based on the FoundationOne CDx assay), and 14 participants had both TMB-H and microsatellite instability–high (MSI-H) disease. Of the 102 participants evaluable for efficacy, the objective response rate (ORR) was 29%, with a median duration of response that was not reached (1). This new approval represents the fourth “tissue agnostic” approval by the FDA, following behind pembrolizumab for mismatch repair (MMR)-deficient solid tumors and larotrectinib and entrectinib for tissue agnostic “rare cancers” (2). The FDA has approved the PD-1 inhibitor, nivolumab (OPDIVO, Bristol-Myers Squibb), for the treatment of non–small cell lung cancer (NSCLC) with tumors harboring a TMB-H phenotype (3, 4). Recognition of tumor neoantigens by host T cells is one of the critical factors predicting immunotherapy response (4). TMB generally correlates with response to anti-PD-1 therapies, supported by a pooled analysis of 27 tumor types (5). There is significant ongoing research to identify the ideal biomarkers to guide immunotherapy selection and management, and this includes characterizing the predictive role of TMB.

TMB can be determined by using different methods, but the optimal approach calculates the mutational load based on exome-wide sequencing analysis encompassing approximately 30 Mb (6). However, the FoundationOne CDx assay estimates TMB on the basis of a more limited gene panel encoded by 0.8 Mb (7). While initial studies have suggested that these gene panel approaches offer reasonable estimates of TMB, concerns regarding the stochastic error inherent to limited gene panel sequencing have been raised (8–10).

The FoundationOne CDx assay determines TMB by counting synonymous and nonsynonymous variants present at 5% allele frequency or greater. According to the product label, TMB scores are impacted by patient-specific factors, such as the site of biopsy (primary or metastatic lesion) and specimen tumor content. Other technical factors also impact the TMB score, including the amount of genome interrogated, filtering of alterations, tumor heterogeneity, and read depth (8). These factors impact reproducibility of TMB scores, even when using the same assay. The challenge of interpreting TMB scores is further complicated by the availability of multiple diagnostic assays. It is unlikely that a single TMB threshold could uniformly be applied to all assays (11, 12). Blood-based cell-free DNA offers a more convenient approach to assess TMB and potentially overcomes the problem of tumor heterogeneity, but fewer clinical studies have validated this approach. In the B-FIRST and MYSTIC trials, blood-based TMB predicted response to immune checkpoint inhibitors in the first-line treatment of non–small cell lung cancer (NSCLC; refs. 13, 14). However, the relationship between TMB scores in tissue and blood remains unclear.

What is TMB?

TMB is a measurement that quantifies the number of muts/Mb harbored by tumor cells. Extensive research has examined TMB as a predictive biomarker of immunotherapy response (2). Compared with tumors with low TMB, tumors with TMB-H tend to have more immunogenic neoantigens (3). Recognition of tumor neoantigens by host T cells is one of the critical factors predicting immunotherapy response (4). TMB generally correlates with response to anti-PD-1 therapies, supported by a pooled analysis of 27 tumor types (5). There is significant ongoing research to identify the ideal biomarkers to guide immunotherapy selection and management, and this includes characterizing the predictive role of TMB.

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Tumor Mutational Burden as an Immunotherapy Biomarker

Translational Relevance
The FDA has approved the programmed cell death protein-1 (PD-1) inhibitor, pembrolizumab, in solid tumors with a tumor mutational burden (TMB) ≥ 10 mutations/megabase based on the FoundationOne CDx assay. However, concerns exist about whether TMB thresholds for predicting response to PD-1 blockade are equivalent across the spectrum of solid tumors, and there are scenarios where high TMB does not predict response. To address the limitations of the TMB, novel biomarkers are needed that account for the immunogenicity of tumor mutations and capture the complexity of the tumor immune microenvironment.

TMB as a Predictive Biomarker of Response in KEYNOTE-158
The FDA approved pembrolizumab for all solid tumors based on the KEYNOTE-158 study, which demonstrated durable responses in patients with a TMB ≥ 10 muts/Mb. However, the approval also raises several concerns: (i) KEYNOTE-158 was not a tumor agnostic study and did not convincingly demonstrate clinical activity across all tumor histologies (1), (ii) TMB is a predictive biomarker in certain tumor types, but the optimal threshold to predict immunotherapy response may vary by tumor histology, and (iii) TMB is a surrogate for other biomarkers that may be more predictive of immune checkpoint inhibitor benefit.

KEYNOTE-158 was a multi-cohort study that was limited to 10 malignancies. On further review of the TMB-H cohort, nearly 90% of enrolled participants had either small cell lung cancer (n = 34), cervical cancer (n = 16), endometrial cancer (n = 15), vulvar cancer (n = 15), or anal cancer (n = 14). Clinical benefit was not consistently demonstrated across all tumor types, which suggests that tumor origin, and by extension, tumor immune microenvironment, may influence clinical response. Whereas patients with TMB-H endometrial cancer had an ORR of 47%, patients with TMB-H anal cancer had an ORR of only 7%. Of note, patients with non-TMB-H anal cancer treated with pembrolizumab had a higher response rate (11%), suggesting that TMB, at least in this tumor histology, did not predict benefit. Low enrollment into other disease cohorts further limits the generalizability of study results.

A further concern regarding KEYNOTE-158 is the lack of broad representation of common tumor histologies. Notably, some of the most common tumor types—breast cancer, prostate cancer, and microsatellite stable (MSS) colorectal cancer—were excluded entirely. The omission of these tumors is likely not accidental. These diseases are notoriously resistant to immune checkpoint blockade, and inclusion of these tumor types may have altered study conclusions. In a retrospective analysis, investigators evaluated the impact of TMB, as measured by the MSK-IMPACT next-generation sequencing assay, on immune checkpoint inhibitor response. In this study, a higher somatic TMB (top quintile in each histology) predicted improved overall survival (OS). However, TMB-H cut-off points varied significantly between histologies, as did immune checkpoint inhibitor benefit (15). In this analysis, survival benefit from immune checkpoint blockade was absent among patients with certain histologies, including breast cancer [estrogen receptor positive (ER+)] and negative (ER−)]. In patients with TMB-H glioma, the trend was toward worse survival. These findings suggest that TMB as a predictor of immunotherapy response varies significantly by tumor histology and that a universal TMB threshold may not be appropriate.

Is It Possible to Have a Single TMB-H Threshold for All Cancer Types?
The origin of the TMB-H threshold used in KEYNOTE-158 (10 muts/Mb by FoundationOne CDx) appears to be based on prior studies conducted in NSCLC. CheckMate 227 was an open-label phase III trial that compared the efficacy of nivolumab plus ipilimumab versus chemotherapy alone in patients with stage IV or recurrent NSCLC (1). In patients with TMB-H disease (≥10 muts/Mb), progression-free survival (PFS) was significantly longer with nivolumab plus ipilimumab than with chemotherapy alone. The advantage of immunotherapy was maintained even in those patients with TMB-H disease lacking PD-L1 expression (PD-L1 < 1%). On the other hand, PFS was similar between immunotherapy and chemotherapy among patients with TMB-low disease. In subsequent analysis, nivolumab plus ipilimumab provided greater clinical benefit than nivolumab monotherapy in patients with TMB-H disease, suggesting a universal TMB threshold may not apply equally to all immune checkpoint inhibitors (16). While a TMB threshold of 10 muts/Mb is a reasonable predictor of response in NSCLC, this threshold is not validated across most other tumor types.

Clinical evidence generated from patients with metastatic colorectal cancer suggests that a different TMB threshold is needed. In an analysis of 22 patients with MSI-H metastatic colorectal cancer treated with immune checkpoint inhibitors, the optimal predictive threshold for TMB-H was estimated between 37 and 41 muts/Mb (17). In patients with MSS colorectal cancer, case reports have also demonstrated the potential of TMB to predict benefit from immune checkpoint blockade (18–20). Still, given the retrospective nature of these reports, they cannot be considered practice changing. In an analysis of more than 5,000 MSS colorectal cancer tumors sequenced with the FoundationOne assay, 2.9% were TMB-H (range, 11.7–707.2 muts/Mb; ref. 19). However, it is unknown whether those patients with TMB-H disease treated with immune checkpoint blockade experienced clinical benefit. Smaller studies in patients with MSS metastatic colorectal cancer have also shown mixed results for TMB as a predictive biomarker. In the Targeted Agent and Profiling Utilization Registry, 27 patients with refractory metastatic colorectal cancer and a TMB of at least 9 muts/Mb received single-agent pembrolizumab. Results were disappointing, with an ORR of 11% and a median PFS of only 9.3 weeks (21). In a phase Ib study conducted in Japan, 24 patients with MSS colorectal cancer were treated with regorafenib plus nivolumab. In total, 8 patients (33%) responded. Using the top quartile as the threshold for TMB-H, there was no relationship between TMB and antitumor response (22). Another randomized study suggested that there might be a role for plasma TMB to predict the response from immune checkpoint blockade. In the Canadian Cancer Trials Group CO.26 Study, 180 patients with refractory metastatic colorectal cancer were randomized to tremelimumab and durvalumab or best supportive care alone (23). Survival favored tremelimumab and durvalumab [HR, 0.72; 90% confidence interval (CI), 0.54–0.97; P = 0.07]. Patients with plasma TMB greater than 28 muts/Mb (21% of MSS patients) had the greatest OS benefit (HR, 0.34; 90% CI, 0.18–0.63; P = 0.004). These results and the plasma TMB threshold need further prospective validation. In other tumor histologies not represented in KEYNOTE-158, for example, melanoma and urothelial cancer, other TMB assays...
Can Patients with Very Low TMB Benefit from Immunotherapy?

In some tumor types, there is evidence that low TMB, not TMB-H, predicts benefit from immune checkpoint blockade. Very low TMB may identify patients with recurrent glioblastoma who have favorable survival responses to immunotherapy (26). It is unclear whether this situation is unique to gliomas. This paradox dependency may be a reflection of the immune-privileged central nervous system (CNS) immune environment.

Individuals with germline MMR defects (Lynch syndrome) are at increased risk of CNS tumors, and these patients also respond to nivolumab (27). On the other hand, several series have shown disappointing results in patients with TMB-H glioblastoma without germline MMR defects (28, 29). In these patients, chemotherapy may increase TMB without promoting a response to PD-1 inhibitors. Tumor heterogeneity may, in part, explain poor response to PD-1 inhibitors in patients with TMB-H disease. Tumor-based TMB analysis from a single core biopsy may not be representative of the patient’s overall TMB score, particularly in cases where chemotherapy and radiation have varied effects in different tumor lesions.

Temozolomide is an alkylating chemotherapy known to promote tumor hypermutability in patients with gliomas (30) and neuroendocrine tumors (31). However, patients with glioma tumors that are TMB-H due to prior alkylating chemotherapy do not respond to PD-1 inhibitors. This was demonstrated in an analysis of 10,294 gliomas with a focus on molecular determinants of mutational burden, with TMB-H defined as ≥17 muts/Mb, described two main pathways to hypermutation (32). The first was constitutional defects in DNA polymerase and MMR genes, and a second more common posttreatment pathway associated with acquired resistance to temozolomide (32). Experimentally, temozolomide-induced damage in glioma cells introduced a hypermutated signature. These gliomas with a hypermutable phenotype lacked T-cell infiltrates, had extensive intratumor heterogeneity, and a low rate of response to PD-1 blockade.

Tumor Immunology and TMB

The pitfalls of a universal TMB cut-off point to guide immune checkpoint inhibitor therapy in all tumor types are further highlighted when the basic biology of genetic mutations and immune cell–tumor cell interactions are considered (33). Tumor types with favorable responses to anti-PD-1 antibody therapy despite relatively low mutational burden, such as polyomavirus-positive Merkel cell carcinoma, renal cell carcinoma, and mesothelioma, suggest that mutation quality is more important than mutation quantity. Indeed, emerging data indicate that not all mutations are equivalent in terms of their immunologic impact. Frameshift mutations, insertion deletion mutations, and mutations influencing RNA splicing are thought to generate more immunogenic neoantigens compared with the more common nonsynonymous single-nucleotide mutations that tend to dominate TMB measurements (7, 34). Additional studies have demonstrated how neoantigen similarity to pathogen-derived antigens may influence tumor immunogenicity and, therefore, their response to checkpoint inhibitor immunotherapy (35). Nevertheless, all of these mutation types are weighted the same in TMB scoring systems. These issues highlight the limitations of TMB as a predictive biomarker for immune checkpoint blockade. However, further evaluation reveals additional deficiencies for TMB as a predictive biomarker. HLA locus heterozygosity, which dictates neoantigen diversity, and mutational clonality have a significant impact on antitumor immunity, yet neither are considered in TMB scoring (36, 37).

Response to PD-1 inhibitors in inflamed tumors differs from that in noninflamed tumors (15), and cancer stemness and intratumoral heterogeneity may have a greater impact on (38) immune response and may better predict immunotherapeutic outcomes than TMB (39). This is supported by data indicating that genetic diversity mediates tumor growth and rejection, effectively linking tumor heterogeneity with patient survival and immune checkpoint inhibitor response (40). As some TMB scores include immunologically irrelevant synonymous mutations, and other TMB algorithms use germline subtraction of published sequence databases, leading to inaccurate TMB scores in underrepresented ethnic groups, the limitations of using TMB alone to guide immunotherapy management are evident (33). This may explain why recent meta-analyses have shown TMB to underperform other biomarkers in predicting anti-PD-1/PD-L1 response (41).

The biochemical and cellular composition of the tumor immune microenvironment are known to play a critical role in regulating antitumor immunity, however, they are also not considered by TMB scoring systems (42). Recent studies have demonstrated select oncogenic signaling pathway alterations associated with diminished T-cell infiltration, including those tumors with β-catenin signaling pathway activation or PTEN loss (43–45). Furthermore, various tumor-mediated mechanisms have been implicated in the recruitment and local differentiation of regulatory T cell and myeloid-derived suppressor cell populations, each involved in playing critical roles in suppressing the development of cytolytic T-cell responses (46–48). Other stromal elements of the tumor, such as cancer-associated fibroblast populations, also impact T-cell infiltration and function (49–51). Finally, genetic mutations that impair antigen processing and presentation by tumors also represent a formidable barrier to effective immune recognition and response (52). This complex interaction between the developing tumor and the host immune system varies dramatically between tumor types and likely during therapy (53, 54). Therefore, it is not surprising that studies have demonstrated a lack of correlation between TMB and the extent of tumor-infiltrating T-cell populations even in more immunogenic tumor types (55). Collectively, when considering the vast array of resistance mechanisms available in the tumor’s arsenal and their variation between tumor types, it suggests that TMB measurements alone provide a unidimensional picture of tumor responsiveness to immune checkpoint blockade, and argues that dynamic TMB cutoffs dependent on tumor type should be considered. Future investigations should integrate a complete TMB scoring system with the immunologic properties of the tumor microenvironment to guide immunotherapy decision-making.

What are the Areas of Future Research in the Field?

The FDA approval of pembrolizumab for TMB-H solid tumors is a call to action to better define biomarkers of immunotherapy sensitivity and resistance. The sequencing of immunotherapies may play an essential role in maximizing the benefit derived from these agents. Patients with cancer often receive cytotoxic and mutagenic chemotherapies that may result in higher TMB. In some cases, a tumor that initially has a low TMB may be converted to TMB-H. Nevertheless, it has been consistently shown that immunotherapies provide more significant clinical benefit in the first-line setting compared with later lines, regardless of TMB score (Table 1).
The recent tumor agnostic approval for pembrolizumab in patients with tumors harboring a TMB ≥10 muts/Mb is expected to lead to a larger number of patients being exposed to anti-PD-1 antibody immunotherapy. While further research is needed to understand whether treatment failure on anti-PD-1 therapy in earlier therapy lines impairs subsequent responses to combination immunotherapy regimens, there is emerging evidence suggesting that second-line treatment with combination immunotherapy regimens is less effective. An example in melanoma would be first-line treatment failure on anti-PD-1 antibody therapy followed by ipilimumab plus nivolumab (56). Data suggest an approximately 30% ORR for ipilimumab plus nivolumab in this anti-PD-1 refractory setting, compared with an ORR of approximately 58% for first-line ipilimumab plus nivolumab (57, 58). A systematic review of response rates in the first versus later lines of immune checkpoint inhibitors was beyond the scope of this perspective article, however, further investigation is warranted to determine whether treatment sequence for PD-1/PD-L1 blockade alters survival outcomes.

The continuous nature of immunotherapy biomarkers further complicates assay development and prospective validation. While a patient with a BRAF wild-type melanoma is highly unlikely to respond to a BRAF inhibitor, a patient with negative PD-L1 expression or a low TMB may still respond to a PD-1 inhibitor. While biomarkers for targeted therapy are reported clinically as positive or negative results, an immunotherapy biomarker represents multiple interdependent and continuous variables that will be difficult to capture using a single biological parameter. Other indicators of immune engagement might prove more valuable to guide immunotherapy management. As an example, the PD-L1–NLRP3 signaling cascade in tumors leads to the release of detectable HSPs and chemokines in the plasma and the recruitment of granulocytic myeloid–derived suppressor cells, driving anti-PD-1 resistance (54). Future immunotherapy biomarkers may need to be described as a matrix of several variables, including TMB and other tumor- or host-derived signatures. Some have suggested developing an immunogram (59) that integrates all components of the host–tumor immune interaction.

While TMB is a significant first step toward predicting immunotherapy response, it has several limitations that constrain its broad application. Further support of research to identify and validate biomarkers of sensitivity and resistance to immunotherapy should be a priority.

Authors’ Disclosures

J.H. Strickler reports grants and personal fees from AbbVie, Amgen, AstraZeneca, Bayer, Genentech/Roche, OncoMed, and Seattle Genetics; personal fees from Celgene, Chengdu Kanghong Biotechnology Co., Merck BioPharma, Natera, Pfizer, and Proteus Digital Health, and grants from Exelixis, Astar, Sanofi, Curegenix, Nektar, Gilead, MacroGenics, and Leup Therapeutics outside the submitted work. B.A. Hanks reports grants from Merck, Tempesn Therapeutics, A’STAR D3, Leup Therapeutics, GlaxoSmithKline, and Sanofi, as well as personal fees from Novartis, Merck, and G3 Therapeutics outside the submitted work. Dr. Hanks has a patent for predictive biomarkers for cancer immunotherapy and methods of using same pending. M. Khasraw has received honoraria from Jackson Laboratory for Genomic Medicine. No other disclosures were reported.

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References


Table 1. Examples of clinical trial results with immune check point inhibitors in different cancers showing that response rates, PFS, and OS are more favorable in the first-line setting.

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Treatment line</th>
<th>Therapy</th>
<th>ORR (%)</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma (56)</td>
<td>Previously untreated (n = 26)</td>
<td>Ipi/nivo</td>
<td>58</td>
<td>15.1</td>
<td>Not reached</td>
</tr>
<tr>
<td></td>
<td>Prior single agent ICI (n = 28)</td>
<td>Ipi/nivo</td>
<td>32</td>
<td>14.1</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>Prior targeted therapy (n = 17)</td>
<td>Ipi/nivo</td>
<td>25</td>
<td>2.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Cervical cancer (60)</td>
<td>Previously untreated (n = 19)</td>
<td>Ipi 1/nivo 3</td>
<td>31.6</td>
<td>13.3</td>
<td>Not reached</td>
</tr>
<tr>
<td></td>
<td>Previously treated (n = 26)</td>
<td>Ipi 1/nivo 3</td>
<td>23.1</td>
<td>3.6</td>
<td>10.3</td>
</tr>
<tr>
<td></td>
<td>Previously untreated (n = 24)</td>
<td>Ipi 3/nivo 1</td>
<td>45.8</td>
<td>8.5</td>
<td>Not reached</td>
</tr>
<tr>
<td></td>
<td>Previously treated (n = 22)</td>
<td>Ipi 3/nivo 1</td>
<td>36.4</td>
<td>5.8</td>
<td>25.4</td>
</tr>
<tr>
<td>NSCLC KEYNOTE-001 (61)</td>
<td>≥ Second line (n = 449)</td>
<td>Pembro</td>
<td>41.6</td>
<td>6.2</td>
<td>22.3</td>
</tr>
<tr>
<td></td>
<td>NSCLC CheckMate-026 (62)</td>
<td>Previously untreated (n = 423)</td>
<td>Nivo vs. doc</td>
<td>26 vs. 33</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>NSCLC CheckMate-063 (63)</td>
<td>≥Third line (n = 117)</td>
<td>Pembro</td>
<td>22.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Abbreviations: Doc, docetaxel; Ipi, Ipilimumab; mOS, median OS; mPFS, median PFS; Nivo, nivolumab; Pembro, pembrolizumab.
Tumor Mutational Burden as an Immunotherapy Biomarker

Tumor Mutational Burden as a Predictor of Immunotherapy Response: Is More Always Better?

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