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Burden of Proof: Evaluating the Efficacy of Tumor Mutational Burden (TMB) in Predicting Response to Immune Checkpoint Inhibitors

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EDITORIAL

Immune checkpoint inhibitors (ICIs) have transformed the standard of care for numerous cancer types. For several patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC), ICIs are an integral component of front line and subsequent line treatments based on multiple clinical trials and category 1 recommendations in the NCCN guidelines [1-9]. These treatments can induce sustained responses in a cohort of patients; however, the magnitude of benefit varies significantly amongst patients and tumor types. A large number of patients are either resistant or only respond temporarily to ICIs. Biomarkers that can help predict which patients may benefit from ICIs are critical since they can uncover a subset of patients who would be good ICI monotherapy candidates and help determine who might benefit from alternative therapies or novel combinations. For instance, programmed death-ligand 1 (PD-L1) expression, a biomarker which has shown to have predictive value in NSCLC patients treated with ICIs, can also be used to identify triple-negative breast cancer patients who could benefit from ICIs [6,10]. However, PD-L1 expression is not predictive of ICI response amongst some other tumor types, such as in melanoma [11]. Moreover, the antibodies used for testing and the way the test results are interpreted are different depending on the checkpoint inhibitors used and the tumor type.

In recent years, other biomarkers have been detected that can predict ICI response regardless of the tumor type. In 2017, pembrolizumab was FDA approved for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors [12]. This was the first tumor agnostic drug approved by the FDA which helped expand the use of ICIs to other cancer patients.

Earlier this year, the FDA approved pembrolizumab for the treatment of patients with tumors that were found to be tumor mutational burden-high (TMB-H) [13]. Interestingly, TMB-H has been found to correlate with ICI response even when PD-L1 expression is absent [14]. There are also reports of ICI benefit when the tumor is microsatellite stable (MSS), but TMB-H [15]. Given this discrepancy, we would like to delve deeper into what is

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TMB and how does it aid our understanding of predicting ICI response?

TMB is defined as a quantitative measure of the total number of somatic non-synonymous mutations per coding area of a tumor genome. It is theorized that the greater amount of mutations present, the higher the likelihood that the tumor will create unique neo-antigens that will be recognized as foreign by the immune system [16]. Since ICIs are used to amplify the immune response, tumors with a greater mutational load are more likely to be affected by this treatment. The prevalence of somatic mutations is highly variable between tumor types. They are most predominant in melanoma and lung cancer which is likely caused by chronic exposure to mutagens in ultraviolet light and tobacco smoke respectively [17]. There are also intrinsic mechanisms that can make a tumor have a higher mutational burden. For instance, defects in mismatch repair (MMR) genes can lead to hyper-mutated tumors, particularly at the sites of microsatellites, which can create an MSI-H phenotype [18]. The association between TMB-H and MSI-H can help explain why MSI-H tumors are responsive to ICIs. In a study of 302 colorectal cancer (CRC) tumors which were MSI-H, 99.7% were found to be also TMB-H [15]. Tumor-based TMB, which was initially measured using whole exome sequencing (WES), can now be accurately assessed in the peripheral blood using platforms such as Foundation One Liquid CDx, Guardant OMNI, and PredicineATLAS [18-21]. Blood-based TMB has also shown to be a reliable predictor of ICI response in multiple studies [22,23]. In summary, TMB is a readily assessable predictive biomarker that should be incorporated in the workup of all advanced solid-tumor malignancies.

A high TMB has been shown in many studies to be an independent marker for ICI response in multiple tumor types. For instance, the results of Keynote-158, which led to the FDA approval of pembrolizumab for TMB-H tumors, evaluated the predictive value of TMB in patients with various tumor types who received pembrolizumab. In the efficacy population, 29% of patients with TMB-H tumors (defined as ≥10 mutations/megabase [mut/Mb]) had an objective response compared to 6% of patients who had non-TMB-H tumors [24]. The predictive nature of TMB could not be explained by the presence of other biomarkers. TMB-H tumors were associated with improved response irrespective of PD-L1 expression. Also, when patients with MSI-H tumors were excluded, 28% of patients with TMB-H tumors had an objective response [24]. This illustrates how TMB alone can identify a subset of patients who can potentially benefit from ICIs. In addition, the likelihood of ICI benefit potentially increases the higher the TMB becomes. In a retrospective analysis which evaluated the relationship between TMB and outcomes in various cancers treated with ICIs, the response rate to anti-programmed cell death protein 1 (PD-1) or anti-PD-L1 monotherapy improved as the TMB increased. The response rate was 4% for low TMB (defined as 1 mut/Mb - 5 mut/Mb), 26% for intermediate TMB (defined as 6 mut/Mb -19 mut/MB), 45% for high TMB (defined as ≥20 mut/Mb), and 67% for very high TMB (defined as >50 mut/Mb) [25]. Thus, the magnitude of TMB is important to keep in mind when testing for this marker.

TMB can also be used to better predict response within MSI-H patients. Among patients with MSI-H tumors, the overall response rate to ICIs in prior studies was found to be 39.6% [26]. Thus, there is a still a large cohort of patients within this enriched population that do not benefit from ICIs. It is important to note that the average TMB in MSS tumors is likely different than the average TMB in MSI-H tumors. For instance, one analysis found the median TMB to be 38.63 in 16 CRC patients with MSI-H tumors compared to 10.39 in 39 CRC patients with MSS tumors [27]. In a study that evaluated 22 CRC patients

with MSI-H tumors, 13/13 (100%) patients with TMB-H (defined as ≥37 mut/Mb - 41 mut/Mb) responded to ICIs while 6/9 (66.7%) patients with low TMB had progressive disease [28]. Overall, TMB can be a predictive marker in both the general and MSI-H populations even though the cut-off values may vary.

A unique population to also consider is MSS/TMB-H patients. Though MSI-H and TMB-H appear to be interrelated, there is still a subgroup of MSS patients that are TMB-H. One study found approximately 3% of MSS CRC tumors to be TMB-H and there are case reports which show ICI benefit in this population [15,29]. This reinforces how TMB can identify additional patients who may benefit from ICIs. This cohort of patients can also provide insight into unique genes that may play a role in ICI response. For instance, the aforementioned study also tried to assess the genes associated with an MSS/TMB-H phenotype in CRC. In the analysis, patients that were MSS/TMB-H were approximately 100x more likely to contain a variant in the POLE gene compared to MSS/TMB-Low patients (20.7% vs 0.2%) [15]. DNA polymerase epsilon (POLE) and delta 1 (POLD1) are DNA proofreading enzymes in which particular mutations can lead to very high rates of base substitution mutations [29]. Both germline and somatic mutations in POLE and POLD1 have been shown to cause a highly mutated, but MSS-type tumor in CRCs and endometrial cancers [29,30]. Since these gene mutations can predispose to a higher TMB, screening for them may potentially find additional patients who would benefit from ICIs. With this in mind, there are clinical trials that are underway that are assessing ICI response in POLE/POLD1-mutated tumors [31-33].

Despite this promise, TMB as a predictive marker for ICI response is not a homerun. The cut-off definitions for TMB-high and low are not uniform. For example, TMB-H was defined as ≥ 10 mut/Mb in the FDA approval given the results of Keynote-158 [13,24]. However, previous studies have had different definitions of TMB-H and have calculated it using different methodologies [34]. It is also important to consider that a high TMB for one tumor may not be considered high for another tumor [35]. In other words, different tumors may need different definitions of TMB-H. It will be imperative to standardize the testing and reporting of TMB-H in studies moving forward and there are currently efforts underway in trying to do so [36].

Overall, ICIs can induce durable responses in a subset of patients and predictive biomarkers are crucial to help identify patients who would benefit from them. The data behind TMB has been promising and provides insight into understanding the likelihood of ICI response. Though this biomarker should continue to be substantiated in different tumor types, TMB adds to previously established biomarkers and should be part of the workup of any patient with advanced cancer.

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