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Authors

Subbiah, V
Solit, DB
Chan, TA
et al.

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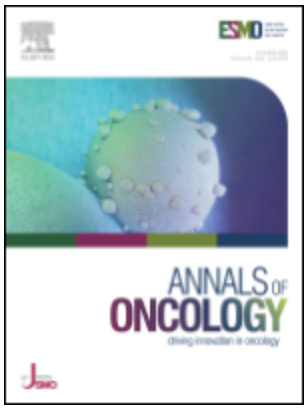

The FDA Approval of Pembrolizumab for Adult and Pediatric Patients with Tumor Mutational Burden (TMB) ≥10: A decision centered on empowering patients and their physicians

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Complete List of Authors:	Subbiah, Vivek; University of Texas MD Anderson Cancer Center, Investigational Cancer Therapeutics Solit, David; Memorial Sloan-Kettering Cancer Center, Medicine Chan, Timothy; Cleveland Clinic Foundation, Center for Immunotherapy and Precision Oncology Kurzrock, Razelle; UC San Diego, Center for Personalized Cancer Therapy
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Table 1: FDA indications for Pembrolizumab (KEYTRUDA) a programmed death receptor-1 (PD-1)-blocking antibody as of June 29h 2020 [19]. Number of indications for the disease in parenthesis. > 15 tumor types and > 20 specific indications.

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1. Melanoma (N=2 indications)

- for the treatment of patients with unresectable or metastatic melanoma.
- for the adjuvant treatment of patients with melanoma with involvement of lymph node(s) following complete resection.

2. Non-Small Cell Lung Cancer (NSCLC) (N=4 indications)

- in combination with pemetrexed and platinum chemotherapy, as first-line treatment of patients with metastatic nonsquamous NSCLC, with no EGFR or ALK genomic tumor aberrations.
- in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, as first-line treatment of patients with metastatic squamous NSCLC.
- as a single agent for the first-line treatment of patients with NSCLC expressing PD-L1 [Tumor Proportion Score (TPS) ≥1%] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is:
  - stage III where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic.
- as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 (TPS ≥1%) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving KEYTRUDA.

3. Small Cell Lung Cancer (SCLC) (N= 1 indication)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

4. Head and Neck Squamous Cell Cancer (HNSCC) (N=3 indications)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

5. Classical Hodgkin Lymphoma (cHL) (N=1 indication)

- for the treatment of adult and pediatric patients with refractory cHL, or who have relapsed after 3 or more prior lines of therapy.

6. Primary Mediastinal Large B-Cell Lymphoma (PMBCL) (N=1 indication)

- for the treatment of adult and pediatric patients with refractory PMBCL, or who have relapsed after 2 or more prior lines of therapy

7. Urothelial Carcinoma (N=3 indications)

- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.
- for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum- containing chemotherapy.
- for the treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

8. Microsatellite Instability-High Cancer (N=2 indications)
    - for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or
    - colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

9. Gastric Cancer (N=1 indication)

- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

10. Esophageal Cancer (N=1 indication)

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one or more prior lines of systemic therapy.

11. Cervical Cancer (N=1 indication)

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.

12. Hepatocellular Carcinoma (HCC) (N=1 indication)

- for the treatment of patients with HCC who have been previously treated with sorafenib.

13. Merkel Cell Carcinoma (MCC) (N=1 indication)

- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.

14. Renal Cell Carcinoma (RCC) (N=1 indication)

- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

15. Endometrial Carcinoma (N=1 indication)

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

16. Tumor Mutational Burden-High (TMB-H) Cancer (N=1 indication)

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

17. Cutaneous Squamous Cell Carcinoma (cSCC) (N=1 indication)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

18. Colorectal Cancer (N=1 indication)

- for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.

The FDA Approval of Pembrolizumab for Adult and Pediatric Patients with Tumor Mutational Burden (TMB) ≥10: *A decision centered on empowering patients and their physicians*

Vivek Subbiah[1], David B. Solit[2], Timothy A. Chan[3] and Razelle Kurzrock[4]

[1] Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Division of Cancer Medicine, UT MD Anderson Cancer Center, Houston, Texas, USA 77030 vsubbiah@mdanderson.org

[2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA. solitd@mskcc.org.

[3]Center for Immunotherapy and Precision Oncology, Taussig Cancer Institute; Lerner Research Institute,Cleveland Clinic Foundation, Cleveland, Ohio, USA chant2@ccf.org

[4]Center for Personalized Cancer Therapy and Division of Hematology and Oncology, University of California San Diego Moores Cancer Center, 3855 Health Sciences Dr, La Jolla, CA, 92093, USA. Electronic address: rkurzrock@ucsd.edu.

Short title: Pembrolizumab FDA approval for TMB≥10

Ref: 19: Table 1.

Corresponding author: Vivek Subbiah, MD; Department of Investigational Cancer Therapeutics (Phase I Clinical Trials Program), Unit 455, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd. Houston, TX 77030. Phone: 713-563-1930 Fax: 713-792-0334. Email: vsubbiah@mdanderson.org

On June 16, 2020, the US Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab for the treatment of "adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options"[1]. This approval was based on efficacy data from 10 refractory solid tumor cohorts enrolled in a multicenter, non-randomized, open-label trial (KEYNOTE-158 (NCT02628067)) [1]. Altogether, 102 patients (13%) had TMB-H tumors, defined as TMB ≥10 mut/Mb. The objective response rate (ORR) was 29% (95% confidence interval (CI): 21,39). Overall, about half the responses were of greater than 2 years with many ongoing, a durability of response rarely observed in heavily pre-treated metastatic cancers with treatment modalities other than immunotherapy.

As it was based on a relatively small single-arm study, the tumor agnostic nature of the pembrolizumab approval has generated considerable debate within the oncology community. Based on first-hand experience with immune checkpoint inhibitors in patients with TMB-H tumors (a subset of whom have gone from a refractory, end-stage state to durable complete remissions lasting years) and from review of the available literature, we strongly support the tumor agnostic FDA approval for pembrolizumab for TMB-H patients. We believe that the approval will facilitate access to a therapy that can result in significant benefit for this molecularly defined subset of patients with no effective alternative treatment options. This approval will especially impact patients with rare cancer types, which in sum constitute ~25% of the cancer burden, and underserved

minority populations which are less likely to have access to tumor molecular profiling or off-label therapies.

This is far from the first FDA approval for pembrolizumab, but rather an expansion of the label of a drug that is already authorized for many indications and whose safety profile is widely known. As of June 29, 2020, pembrolizumab has been FDA-approved for >15 indications (>20 specific labels) (**Table 1**). As with all biologic and targeted cancer therapies, not all patients treated with pembrolizumab (even in the tumor types approved) achieve a durable response, and biomarkers will be critical to optimizing the use of this agent by allowing clinicians to identify those patients most likely to benefit. Previously, only PD-L1 expression and microsatellite instability high/deficient mismatch repair (MSI-H/dMMR) were recognized by FDA as predictive biomarker of immunotherapy response. An association between TMB-H and response to anti-PD-1/PD-L1 therapies initially arose out of retrospective studies and has also been observed in analyses of real world datasets [2-11] A recent meta-analysis of 117 clinical trials (12,450 patients treated with immunotherapy), revealed that TMB-H (including TMB with cut off $\geq$10 mut/mb) was significantly associated with enhanced ORR for anti-PD-(L)1, anti-CTLA-4, and combinations ($p<0.0001$ for all) [12]. Furthermore, MSI-H appears to be associated with immunotherapy response largely because it results in high TMB; further, patients with TMB-H tumors without MSI-H respond as well to anti-PD-(L)1 therapies as MSI-H patients.[11]

There is strong biologic rationale for TMB-H as a biomarker for immunotherapy sensitivity. In the most general sense, TMB refers to the total number of mutational events in the genome of a tumor. The operational definition of TMB has differed

between studies, but all TMB definition variations aim to summate the number of somatic alterations in a given tumor. One commonly used definition of TMB refers to the total number of nonsynonymous mutations per coding area of tumor genome analyzed by the specific assay employed. Higher TMB is associated with greater neoantigen burden, which activates T lymphocytes inducing them to proliferate and kill cancer cells [5]. The greater the number of neoantigens, the greater the extent of "non-self" that can be recognized by T cells. As such, TMB is a measurement of the fundamental genetic basis of anti-tumor rejection potential. As a biomarker, it quantifies the targets of cancer immunotherapy themselves – the somatic tumor mutations – which cumulatively form the basis of anti-tumor rejection. TMB is a more direct measure of tumor rejection potential than MSI assays, which detects the presence of microsatellite alterations and do not quantify the mutations themselves. TMB has been shown to be one of the most essential factors that determine the success of immune checkpoint blockade treatment [13].

There is thus strong scientific and clinical data beyond those from KEYNOTE-158 supporting an association between TMB-H and immunotherapy response. There is however debate as to the optimal method for quantitating TMB [14]. Retrospective studies suggest that there is a linear relationship between TMB and outcome [2]. The optimal cutoff for defining high TMB may also vary among cancer types. The TMB≥10 threshold arose as a consensus recommendation from the TMB harmonization consortium (a multi-stakeholder consortium of academia, pharma, non-profit, cancer society representatives, commercial sequencing companies and non-profit patient advocate groups) with recognition that it may not be optimal for all clinical scenarios.

Understanding other biological variables that affect immune activation, including host factors such as major histocompatibility presentation, will likely further strengthen the predictive value of TMB in the future [5]. Greater HLA diversity enables better control of both infectious disease and cancer following immune checkpoint therapy by expanding the size of the immunopeptidome [15]. Greater HLA diversity enables presentation of more neopeptides, and hence works in conjunction with TMB to enable immune checkpoint efficacy. It is likely that consideration of additional patient and tumor-specific factors such as HLA will enable refinement of the predictive value of TMB. As with any complex biological process, anti-tumor immunity is associated with multiple biomarkers and several biomarkers will likely be needed to increase the sensitivity and specificity of predictive models. Nowhere is this clearer than in breast cancer oncology, where the successive discovery and implementation of ER, PR, Her2/neu, BRCA1/2, etc. over time has refined clinical treatment paradigms. Furthermore, as we have seen repeatedly, continuous variables such as the Oncotype DX® risk score, PD-L1 expression levels, and TMB, are honed as our knowledge deepens. It was important, therefore, to not let the immediate pursuit of perfection prevent progress.

Undoubtedly, the TMB approval will fuel further research that will enhance our predictive capabilities. However, based on what we already know about immunotherapy benefit for TMB≥10 tumors, these deliberations will likely take many years, especially if the intent is to prospectively design studies to determine TMB thresholds for each cancer type. Furthermore, as such prospective studies are likely not

feasible for many rarer cancers, it is our opinion that the completion of such studies should not be used as a pretext to restrict access to a life-saving drug.

One concern that has been brought up is that the FDA approval of pembrolizumab for cancers with TMB≥10 will prevent patients from receiving other potentially better treatments. It is important to emphasize that the FDA does not dictate standards of care: it provides patients with options. The FDA has approved pembrolizumab for patients with a TMB≥10 who have "progressed following prior treatment and who have no satisfactory alternative treatment options." Clearly, if there are more effective and less toxic treatments available for patients with metastatic malignancies who have progressed on fourth or fifth-line therapy, the oncologist can judiciously elect to use those options.

The successes of immunotherapy are grounded in the marriage between genomics and immunology [16-18]. Cancer is a genetic disease and tumor genomic profiling is increasingly recognized as critical to ensuring the correct diagnosis of an individual patient's tumor type [16]. Every patient with cancer deserves an accurate diagnosis, including knowing whether their tumor harbors therapeutically actionable mutations or mutational signatures such as MSI-H or TMB-H[16]. Since there is no way to know *a priori* whether or not a tumor is TMB-H, an indirect (or direct) advantage of this approval is that more cancer patients will receive genomic testing and hence an accurate cancer diagnosis[17].

We also believe that lack of access to molecular profiling technologies and off-label use of targeted and immunotherapies is becoming an increasingly important contributor to health care disparities. We are thus hopeful that the FDA approval of

pembrolizumab for TMB-H will help reduce such disparities by expanding reimbursement for tumor molecular profiling and by facilitating access to a widely used therapy that can induce durable responses in this molecularly defined population. Previously, the only access to immunotherapy for many rare cancer patients with TMB-H who had exhausted standard-of-care therapy was referral for a clinical trial. If the patient was not eligible for the trial, or could not afford to travel long distances, this option was closed to the patient. Requests for off label use are also only rarely successful and can cause significant delays in treatment. Undoubtedly, these logistical considerations and hurdles create disparities that most significantly impact those cancer patients of lower socioeconomic status with a disproportionate impact on underserved minority populations. The expanded FDA indication for pembrolizumab, by permitting broader access to the drug, helps to level the field for patients from all walks of life.

In summary, the tissue-agnostic FDA approval of TMB≥10 mut/mb for pembrolizumab has transformative importance for multiple reasons: (i) the magnitude and durability of responses mean that the approval will be life-saving for a subset of patients with lethal cancers; (ii) drug access and reimbursement will be enhanced for patients with pediatric and rare adult solid tumors, an enormous unmet need; (iii) physicians and patients will be empowered to make decisions in the real world; (iv) immunotherapy access will be improved for underserved minority and economically disadvantaged populations; and (v) the approval will encourage adoption of modern/essential diagnostic genomic sequencing tests. Therefore, we believe that the FDA-approval of pembrolizumab is based on compelling scientific rationale and clinical data and that it will provide refractory adult and pediatric cancer patients who, without

this treatment would undoubtedly die of their cancer, a therapeutic option that can confer long-term durable remissions and the gift of time.

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D.B.Solit has consulted for/received honoraria from Loxo Oncology, Lilly Oncology, Pfizer, Vivideon Therapeutics, Q.E.D. Therapeutics and Illumina.

TA Chan is a co-founder of Gritstone Oncology and holds stock. Dr. Chan receives research funding from BMS, Pfizer, Illumina, Eisai, AstraZeneca, NysnoBio. He is a paid consultant of BMS, Illumina, AstraZeneca, An2H. Dr. Chan holds patents for the use of TMB for prediction of clinical benefit from immune checkpoint inhibitors and receives royalties.

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3. Small Cell Lung Cancer (SCLC) (N= 1 indication)

- for the treatment of patients with metastatic SCLC with disease progression on or after platinum-based chemotherapy and at least one other prior line of therapy.

4. Head and Neck Squamous Cell Cancer (HNSCC) (N=3 indications)

- in combination with platinum and FU for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC.
- as a single agent for the first-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.
- as a single agent for the treatment of patients with recurrent or metastatic HNSCC with disease

progression on or after platinum-containing chemotherapy.

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- for the treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test, with disease progression on or after 2 or more prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy.

10. Esophageal Cancer (N=1 indication)

- for the treatment of patients with recurrent locally advanced or metastatic squamous cell carcinoma of the esophagus whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA-approved test, with disease progression after one

or more prior lines of systemic therapy.

11. Cervical Cancer (N=1 indication)

- for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA-approved test.

12. Hepatocellular Carcinoma (HCC) (N=1 indication)

- for the treatment of patients with HCC who have been previously treated with sorafenib.

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- for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma.

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- in combination with axitinib, for the first-line treatment of patients with advanced RCC.

15. Endometrial Carcinoma (N=1 indication)

- in combination with lenvatinib, for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation.

16. Tumor Mutational Burden-High (TMB-H) Cancer (N=1 indication)

- for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.
- Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established.

17. Cutaneous Squamous Cell Carcinoma (cSCC) (N=1 indication)

- for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

18. Colorectal Cancer (N=1 indication)

- for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer

Adult Indications: Additional Dosing Regimen of 400 mg Every 6 Weeks

- for use at an additional recommended dosage of 400 mg every 6 weeks for all approved adult indications.

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