FDA Approval Summary: Pembrolizumab for the Treatment of Tumor Mutational Burden–High Solid Tumors

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ABSTRACT

The FDA approved pembrolizumab on June 16, 2020, 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. FDA granted the approval based on a clinically important overall response rate (29%; 95% confidence interval, 21–39) and duration of response (57% of responses lasting ≥ 12 months) in the subset of patients with TMB-H solid tumors ($n = 102$) spanning nine different tumor types enrolled in a multicenter single-arm trial (KEYNOTE-158). The efficacy of pembrolizumab was supported by the results of whole-exome sequencing (WES) analyses of TMB in additional patients enrolled across multiple pembrolizumab clinical trials, and a scientific understanding of the effects of PD-1 inhibition. Overall, the adverse event profile of pembrolizumab was similar to the adverse event profile observed in prior trials that supported the approval of pembrolizumab in other indications. This approval of pembrolizumab is the first time that the FDA has approved a cancer treatment for an indication based on TMB, and the fourth based on the presence of a biomarker rather than the primary site of origin.

Introduction

The FDA granted accelerated approval to pembrolizumab on June 16, 2020, 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. This article summarizes pre-application interactions, the FDA's review of data submitted in the supplemental biologics licensing application (sBLA), and the basis for approval.

Background on TMB-H

Similar to microsatellite instability–high (MSI-H) or mismatch repair–deficient (dMMR) cancers, which typically express a large number of neoantigens (1, 2), TMB reflects the overall somatic genomic burden of mutations within a given tumor. Multiple reports indicated that a higher mutational burden appears to increase the likelihood of neoantigen formation and the potential for immune system recognition (3–5). TMB differs across tumor types, and variability within tumor types has been observed (6). A TMB score of ≥10 mut/Mb has been proposed as a threshold with a high likelihood of neoantigen formation, and therefore defining TMB-H status (7). A key consideration for defining TMB-H is that different assays may identify different patient populations; for example, assays may differ with respect to panel size, gene content, germline filtering, and bioinformatic TMB algorithms.

Regulatory History

The FDA approved pembrolizumab on May 23, 2017, for the treatment of adult and pediatric patients with unresectable or metastatic, MSI-H, or dMMR solid tumors that progressed following prior treatment and who have no satisfactory alternative treatment options (8). This was the first tissue-agnostic approval, based on demonstration of a clinically meaningful objective response rate, with subsequent tissue agnostic development of drugs for other biomarkers including *NTRK* and TMB. Multiple broad stakeholder meetings were held as part of the Friends of Cancer Research (FOCR) TMB harmonization project (9). On the basis of data presented during these meetings, industry sponsors proposed 10 mut/Mb as the lower bound of an "equivocal zone", or a cut-off point that would identify patients with TMB-high tumors (≥10 mut/Mb; ref. 9). FDA agreed that a lower bound of 10 mut/Mb was reasonable for clinical trial enrollment for a study evaluating a pan-tumor indication and for the selection of an analysis population for statistical planning purposes; however, FDA cautioned that an assessment of this approach would be evaluated in the context of a submission for regulatory purposes and a clinical trial would be necessary to support a new tissue agnostic indication for TMB-H tumors.

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Table 1. Pembrolizumab trial in TMB-H cancer.

Clinical trial	NCT no.	Trial design	Regimen/ schedule/route	Study endpoints	Treatment duration/ follow up	No. of patients enrolled	Study population
KEYNOTE-158	02628067	Non-randomized, multi-center, open-label	Pembrolizumab 200 mg intravenously every 3 weeks	Primary: ORR per RECIST 1.1 criteria, as assessed by independent central radiology review. Secondary: DOR, PFS, OS, and safety	Up to 2 years of treatment. Patients continued pembrolizumab until one or more of the discontinuation conditions in the protocol were met. All patients were followed up for OS until death, withdrawal of consent, or the end of the study.	1,073	Patients with multiple types of advanced (unresectable and/ or metastatic) rare solid tumors as defined in the protocol

Abbreviations: DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Clinical Trials

This application included tumor response data in patients with whole-exome sequencing (WES)-derived TMB scores across several global studies and also included data on the clinical effects of pembrolizumab in a prospectively planned retrospective analysis of patients enrolled in a multicohort clinical trial (KEYNOTE-158, NCT 02628067; **Table 1**).

KEYNOTE-158 is an open-label, nonrandomized, multicenter, multicohort trial of pembrolizumab in patients with multiple types of advanced (unresectable or metastatic) cancers that progressed following prior treatment and who had no satisfactory alternative treatments. The Investigators' results of KEYNOTE-158 have been published (10). The licensing application included data from 10 cohorts (A through J) and patients received pembrolizumab 200 mg every 3 weeks until unacceptable toxicity or disease progression. The primary efficacy outcome measure was overall response rate (ORR) according to RECIST 1.1 as assessed by blinded independent central radiology (BICR) review. The statistical analysis plan prespecified ≥10 and ≥13 mut/Mb using the FoundationOne CDx assay (F1CDx) as cut-off points to define the TMB-H population. Testing of TMB was blinded to clinical outcomes. The efficacy analysis population consisted of 1,050 patients who received at least one dose of pembrolizumab. TMB scores were missing in 260 of the 1,050 patients (25%) due to reasons including quality control and pathology review issues, sample unavailability, and lack of consent for TMB analysis. Among the 790 patients who met criteria for TMB assessment, a total of 102 (13%) were TMB-H, defined as TMB ≥10 mut/Mb.

The supportive retrospective WES analyses were conducted using pooled data from 12 studies across 24 tumor types with tissue available for TMB assessment. These results were presented by Merck at the 2020 AACR meeting but are not published to date (11). TMB was assessed as the number of nonsynonymous single-nucleotide variants and indels found in protein-coding regions. The studies (KEYNOTE-001, 002, -010, -012, -028, -045, -055, -059, -061, -086, -100, 199) generally administered pembrolizumab as monotherapy or compared pembrolizumab monotherapy to chemotherapy. A total of 2,234 patients had available WES TMB results: 1,772 pembrolizumab-treated patients and 462 chemotherapy-treated patients (enrolled in KEYNOTE-010, -045, or -061). Among the 1,772 pembrolizumab-treated patients, 433 (24%) had WES TMB ≥175 mut/exome (approximately equivalent to ≥10 mut/Mb by F1CDx).

Results

Treatment with pembrolizumab resulted in an ORR of 29.4% [95% confidence interval (CI), 20.8–39.3] per RECIST v1.1, modified to follow a maximum of 10 target lesions and a maximum of 5 target lesions per organ, as assessed by BICR in patients with TMB ≥10 mut/Mb ($n = 102$). Four (3.9%) of the responding patients had a complete response (CR) and the remainder (26 patients or 25.5%) had a partial response (PR). In contrast, a lower ORR of 6.3% (95% CI, 4.6–8.3) was observed in patients with a TMB < 10 mut/Mb ($n = 688$). Median duration of response (DOR) was not reached in the TMB-H population at the time of data cutoff based on Kaplan–Meier estimation (range 2.2+ to 34.8+ months). Most (66.6%) responders had a DOR of ≥24 months. Responses were observed across eight tumor types (**Table 2**). In an exploratory analysis of 32 patients whose tumors had TMB ≥10 mut/Mb and <13 mut/Mb, the ORR was 13% (95% CI, 4–29), including two CRs and two PRs, whereas the ORR in 70 patients with a TMB ≥13 mut/Mb was 37% (95% CI, 26–50).

Table 2. Overall response rate by tumor type in TMB-H (TMB ≥10 mut/Mb; ref. 8).

Tumor type	Patients $N = 102$	ORR %	ORR 95% CI	Duration of response range (months)
Small cell lung cancer	34	29	15–47	4.1–32.5+
Cervical cancer	16	31	11–59	3.7+–34.8+
Endometrial cancer	15	47	21–73	8.4+–33.9+
Anal cancer	14	7	0.2–34	18.8+
Vulvar cancer	12	17	2–48	8.8–11.0
Neuroendocrine cancer	5	40	5–85	2.2+–32.6+
Salivary cancer	3	PR, SD, PD		31.3+
Thyroid cancer	2	CR, CR		8.2–33.2+
Mesothelioma cancer	1	PD		

Abbreviations: CI, confidence interval; CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; TMB-H, tumor mutation burden high.

Table 3. Overall response rate by tumor type in WES analysis.

	Pembrolizumab ORR			
	WES ≥ 175 mut/exome		WES < 175 mut/exome	
	N	ORR (95% CI)	*N*	ORR (95% CI)
Melanoma	43	58 (42–73)	33	9 (2–24)
NSCLC	158	30 (23–38)	165	13 (8–19)
Bladder/urothelial	61	34 (23–48)	137	16 (10–23)
HNSCC	59	24 (14–37)	176	15 (10–21)
Gastric	53	34 (22–48)	261	7 (4–11)
TNBC	22	18 (5–40)	115	3 (1–7)
Ovarian	12	17 (2–48)	281	7 (5–11)
Prostate	11	9 (0–41)	115	6 (2–12)
Other	14	21 (5–51)	56	11 (4–22)

Abbreviations: HNSCC, head and neck squamous cell cancer; NSCLC, non–small cell lung cancer; TNBC, triple-negative breast cancer.

Consistent with the efficacy results in the TMB-H population in KEYNOTE-158, the response to pembrolizumab was higher in the WES TMB ≥175 mut/exome population compared with <175 mut/exome population, with an observed ORR of 31.4% (95% CI, 27.1–36.0) by BICR versus 9.5% in the WES TMB < 175 mut/exome group. In the Kaplan–Meier estimate, more than half of the at-risk responding patients had DOR > 24 months. ORR was 30.3% among 412 patients in the microsatellite-stable TMB-H group (vs. 52.4% among 21 patients with MSI-H tumors that were all TMB-H). The response rates in each tumor type are listed in **Table 3** below. In addition to the response assessments, FDA also reviewed the results of supportive exploratory *post hoc* analyses of progression-free survival (PFS) and overall survival (OS) by TMB when pembrolizumab was compared with chemotherapy in randomized trials KEYNOTE-010 (NSCLC), KEYNOTE-045 (urothelial), and KEYNOTE-061 (gastric). These exploratory analyses showed numerically lower HRs for PFS and OS compared with those observed in the WES TMB < 175 mut/exome subgroups (**Table 4**).

The adverse reaction profile of pembrolizumab is established and the risks of pembrolizumab include immune-mediated adverse reactions such as immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis, and skin adverse reactions (8). The safety profile of pembrolizumab in this population was similar to that described in the Keytruda product labeling (8).

Regulatory Insights

The approval of pembrolizumab for TMB-H cancers represents the fourth time a drug has been approved on the basis of a shared biomarker rather than by primary cancer type defined by histology and anatomic site. Contemporaneously with the approval of pembrolizumab for the TMB-H indication, the FDA approved a supplemental premarket approval (sPMA) application for the F1CDx assay to include a companion diagnostic indication for TMB-H solid tumors at the cut-off point of 10 mut/Mb (P170019/S016; ref. 12). The FDA considered the data available at the time the applications were submitted, including clinical trial results and supportive scientific data that TMB-H status appears to enrich for an immune response to pembrolizumab treatment.

Although labeling for the TMB indication is limited to a description of data from KEYNOTE-158, the application was strengthened by (i) analyses demonstrating a similar ORR in a retrospective analysis of 433 patients with WES TMB ≥175 mut/exome tumors who received pembrolizumab as monotherapy (WES TMB ≥175 mut/exome approximately equivalent to ≥10 mut/Mb by F1CDx), (ii) exploratory *post hoc* analyses of PFS and OS in three randomized trials, (iii) extensive safety characterization of pembrolizumab, and (iv) favorable risk–benefit assessments of pembrolizumab in other cancer types with similar response rates and comparatively high mutational burden (e.g., metastatic melanoma). This approval represents an extension of the use of pembrolizumab, and was specifically targeted to patients without other available treatment options.

In the application, FDA considered the consistency of effects across studied tumors and unmet need for treatments for patients without available therapy. Some variation in antitumor activity (ORR and response duration) may exist in different TMB-H tumor types based on chance, distribution of TMB in the cancers, disease burden, or other factors such as tumor microenvironment, including the immune milieu of the tumor, or likelihood of neoantigen formation due to different causes of TMB (e.g., MSI, sun exposure, smoking; ref. 13). Exploratory analyses of ORR, however, generally supported the relative consistency of treatment effect across tumor types, both in KEYNOTE-158 and the WES analyses, with the possible exception of anal cancer in KEYNOTE-158 ($n = 14$). The 95% CI around the point estimate of 7% for ORR in anal cancer (0.2–34) was wide, reflecting uncertainty regarding the treatment effect. Furthermore, the results in anal cancer may have been influenced by the distribution of TMB in this disease [e.g., few (5) patients with TMB ≥13 mut/MB] or missing TMB information in 3 patients with anal cancer who responded. Although we considered the results across tumors as generally consistent, a limitation is that much of the data is derived from select tumor types. This uncertainty is weighed against the unmet medical need of the populations and additional data from disease-specific subtypes that will be obtained through prospective post-marketing studies.

In assessing the appropriateness of the 10 mut/Mb cut-off point, FDA recognized that TMB is a continuous biomarker and as such, selection of a higher cut-off point may exclude patients from treatment but result in a higher ORR, whereas a lower cut-off point may result in patients receiving treatment with a reduced chance of benefiting. Indeed, some of the observed variability in treatment effects in this

Table 4. HR and 95% CIs of exploratory subgroup analyses of PFS and OS in randomized controlled trials by WES status.

	Pembrolizumab versus chemotherapy			
	WES ≥ 175 mut/exome		WES < 175 mut/exome	
Study	PFS	OS	PFS	OS
KN-010	0.59 (0.40–0.87)	0.56 (0.38–0.83)	1.09 (0.72–1.63)	0.85 (0.56–1.30)
KN-045	0.62 (0.40–0.96)	0.63 (0.40–1.00)	1.13 (0.87–1.47)	0.71 (0.54–0.94)
KN-061	0.73 (0.44–1.22)	0.46 (0.27–0.81)	1.78 (1.43–2.22)	1.12 (0.90–1.41)

application (and in other reports) across tumors may be due to the variable distribution of TMB across cancer types (e.g., with melanoma and lung cancer having more patients at the higher end of the spectrum). Approval based on a cut-off point of 10 mut/Mb denoting TMB-high status was based on information in the application including Merck's data of drug effects in patients above this cut-off point, high unmet need, biological rationale, the prespecified analysis plan, clinical results, and overall risk–benefit considerations. TMB ≥10 mut/Mb represented the cut-off point identified in the non–KEYNOTE-158 "training" dataset and prespecified in the KEYNOTE-158 statistical analysis plan. TMB ≥10 mut/Mb was also a cut-off point identified in prior multi-stakeholder meetings held through the FOCR TMB harmonization project (9).

Among the 70 patients enrolled in KEYNOTE-158 with cancers whose TMB score was ≥ 13 mut/Mb, the estimated ORR was 37% (95% CI, 26–50); in contrast, the estimated ORR in the subgroup of 32 patients whose cancer TMB score was ≥10 mut/Mb but <13 mut/Mb was 13% (95% CI, 4–29). To better characterize the effect on ORR in patients with TMB ≥ 10 mut/Mb and < 13 mut/Mb and assess benefit in this subgroup, Merck is conducting a required postmarketing study to evaluate response and durability in additional patients at these cut-off points. Although the size of this subgroup in KEYNOTE-158 was limited, labeling describes the lower response rate to provide additional information to guide clinical decision-making. As pembrolizumab received accelerated approval, the potential exists to modify the indication to reflect specific cancer types and/or modify the cut-off point if additional data indicate that 10 mut/Mb is not supported from a tissue agnostic perspective.

FDA considered the overall response rate of 29% in patients with TMB ≥10 mut/Mb, and duration of response of 12 months or longer in 57% (including durable complete responses) of responding patients to be clinically meaningful. Depending on context, FDA has granted accelerated or regular approvals for the treatment of advanced cancers where there is a large absolute magnitude of improvement in progression-free survival or in certain instances, a high response rate that is durable when the overall benefit–risk profile is favorable (14, 15). Especially in some rare tumor types, a requirement for randomized trials demonstrating improvements in OS would be challenging to conduct given the frequency of TMB-H disease and the availability of checkpoint inhibitors allowing for potential cross-over upon or prior to progression.

The ORR in the TMB-H population did not appear to be solely driven by MSI-H or PD-L1 status. The pooled response rate in this population in KEYNOTE-158 was similar when patients with MSI-H ($n = 14$) tumors were excluded from the TMB-H group (26.1% after exclusion of patients with MSI-H vs. 29.4% in the total TMB-H population). Antitumor activity was also observed in both patients with PD-L1–positive (CPS ≥1) and PD-L1–negative (CPS <1) tumors within the TMB-H population (35.3% vs. 20.7%, respectively). Antitumor activity in the non–TMB-H population in both patients with PD-L1–positive and PD-L1–negative status was 8.6% versus 3.3%, respectively. Similar results were reported in the WES dataset.

Another review issue was missing TMB information for approximately a quarter of patients in KEYNOTE-158. Even though ORR results were similar (ORR: 9% vs. 10%) for the group of patients whose TMB score was available ($n = 790$) and the group whose TMB score was missing ($n = 260$), the assessment of the impact of the missing data is challenging due to the limited information on the reasons for this missing information. Exploratory sensitivity analyses with imputations of missing TMB scores appeared to support the efficacy conclusions.

As a condition of this approval, Merck agreed to an accelerated approval postmarketing requirement (PMR) to prospectively enroll additional patients to provide information regarding less studied disease types and to further confirm the appropriate cut-off point particularly in histologic tumor types such as CNS tumors and other rare TMB-H cancers, including pediatric cancers. In addition, because of the uncertainty regarding response to pembrolizumab in TMB-H, MSI-H, or dMMR tumors in patients with high-grade gliomas who received prior temozolomide (e.g., whether the entire tumor is TMB-H; ref. 16), product labeling for pembrolizumab recommends testing for these biomarkers using primary glioma specimens obtained prior to initiation of temozolomide (8).

Published data after the FDA approval questioned certain aspects of the approval with respect to disease types approved or cut-off point (17–19). Uncertainties regarding tissue agnostic accelerated approvals, including limited numbers of patients in certain tumor types needs to be balanced against the context of unmet medical need (e.g., patients without satisfactory available therapy). As with any accelerated approval, the potential exists for future modification or withdrawal of the indication. For pembrolizumab, additional prospective data are currently being collected that will help to determine whether the original indication should be retained or modified or whether a higher TMB threshold would be more appropriate.

Although uncertainties exist, including whether there is a "perfect" TMB cut-off point, accelerated approval of pembrolizumab which was based on data in an application that included durable responses, acceptable safety, and a favorable risk–benefit profile, will allow for a treatment option to patients with rare TMB-H cancers without alternative satisfactory treatment options while additional data are obtained via a PMR.

Authors' Disclosures

No disclosures were reported.

Disclaimer

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