Clinical Cancer Research

FDA Approval Summary: Pembrolizumab for the Treatment of Microsatellite Instability-High Solid Tumors

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Abstract

The FDA approved pembrolizumab on May 23, 2017, for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and for the treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. The FDA granted the approval based on an understanding of the biology of MSI-H/dMMR across different tumors along with the clinically important effects on overall response rate (ORR) observed in patients who were enrolled in 1 of 5 single-arm clinical trials. The ORR was 39.6% among 149 patients with 15 different tumor types (95% confidence interval, 31.7–47.9), with a 7% complete response rate. The duration of response ranged from 1.6+ months to 22.7+ months, with 78% of responses lasting $\geq$6 months. Overall, the adverse event profile of pembrolizumab was similar to the adverse event profile observed across 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 a common biomarker rather than the primary site of origin.

Introduction

Pembrolizumab is a mAb that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway–mediated inhibition of the immune response, including the antitumor immune response (1). Blockade of this pathway with antibodies to PD-1 or its ligands has led to clinical responses in patients with multiple different types of cancer, including melanomas, non–small-cell lung cancer, renal-cell carcinoma, bladder cancer, and Hodgkin lymphoma (2). It was hypothesized that checkpoint inhibitors such as pembrolizumab might have antitumor effects across multiple tumor types with a common immune-mediated mechanism of action. The FDA granted accelerated approval to pembrolizumab on May 23, 2017, for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and for the treatment of unresectable or metastatic MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This is the first time that the FDA has approved a cancer treatment for an indication based on a common biomarker rather than the primary site of origin. This article summarizes presubmission interaction with the FDA, the FDA's review of data submitted in the supplemental biologics licensing application (sBLA), issues identified during the review, and the basis for approval.

Regulatory History

The FDA met with Merck in May 2015 (Fig. 1) to discuss the results of Study KEYNOTE (KN)-016. Responses were reported in 4 of 10 pembrolizumab-treated patients with MSI-H colorectal cancer and 5 of 7 patients with other MSI-H tumors, whereas none of 18 patients with microsatellite stable (MSS) colorectal cancer responded (2). On the basis of these preliminary findings, the FDA encouraged Merck to seek Breakthrough Therapy Designation for pembrolizumab for the treatment of patients with MSI-H metastatic colorectal cancer (mCRC; granted in October 2015) and to evaluate the activity of pembrolizumab broadly across MSI-H or dMMR solid tumors. Merck initiated one trial, KN-164, in patients with unresectable or metastatic MSI-H/dMMR colorectal cancer and KN-158, in patients with MSI-H/dMMR non-colorectal tumors.

In March 2016, Merck notified the FDA that accrual was completed in KN-164 and that Merck amended KN-164 to include a new cohort of patients with MSI-H/dMMR mCRC with disease progression after one fluorouracil-based regimen in the metastatic setting. In April 2016, Merck provided the FDA with an update of the MSI-H development program. In July 2016 (slightly more than one year after the preliminary KN-016 results were

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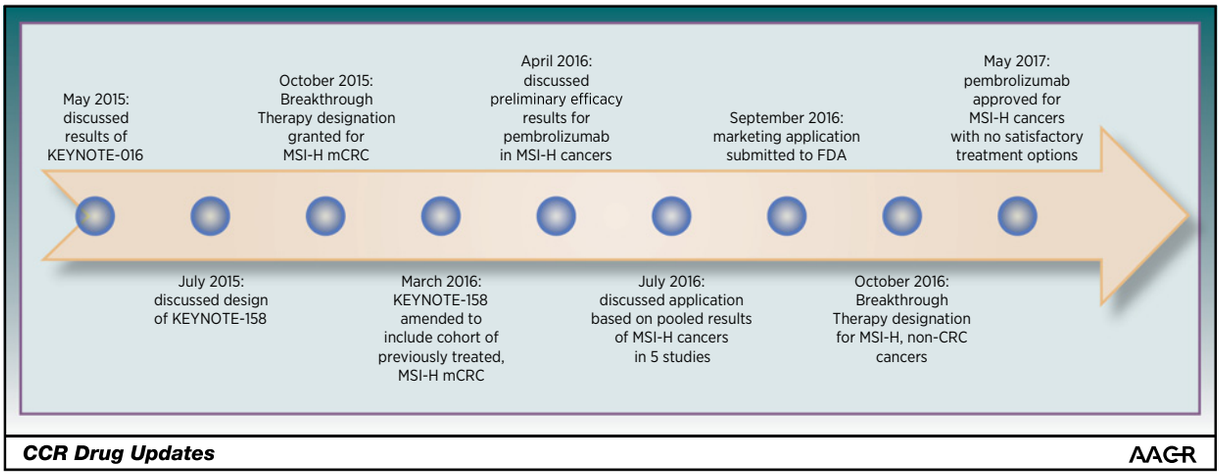

Figure 1.
Timeline of events for pembrolizumab MSI-H/dMMR application. CRC, colorectal cancer; mCRC, metastatic colorectal cancer.

published), the FDA and Merck held a meeting to discuss submission of a supplement to the sBLA based on a pooled analysis of patients with MSI-H/dMMR tumors across 5 clinical trials, including the interim results of KN-164 and KN-158. The FDA informed Merck of the Agency's willingness to consider granting accelerated approval based on durable overall responses rates (ORR) in a relapsed/refractory, biomarker-defined, tumor site–agnostic indication. The sBLA was submitted on September 8, 2016. The FDA granted Breakthrough Therapy designation to pembrolizumab in October 2016 for non-colorectal cancer, MSI-H/dMMR cancers; this was the first Breakthrough Therapy designation granted for a tumor site–agnostic indication.

Background on MSI-H/dMMR

Mismatch repair deficiency usually occurs due to mutations that code for genes of mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) that are responsible for recognizing and correcting errors in mismatched nucleotides or through methylation of the MLH1 gene promoter. These errors in MMR lead to microsatellite instability (MSI) due to the accumulations in errors in DNA microsatellites (short repetitive sequences in DNA; ref. 3). Because of greatly increased numbers of somatic mutations, MSI-H tumors express a large number of neoantigens, potentially rendering them more susceptible to immunotherapy than tumors with few mutations (4–6). Patients with MSI-H tumors responding to pembrolizumab develop a rapid *in vivo* expansion of neoantigen-specific T-cell clones; these clones were reactive to neoantigens found in the patients' tumors (7).

MSI-H or dMMR is observed in many primary cancers (7). In addition to sharing a hypermutated phenotype, MSI-H cancers across different histologies share common histopathologic characteristics, including lymphocytic and other immune cell infiltration, medullary histology, and poorly differentiated histology (8). The incidence of MSI-H or dMMR has largely been determined in patients undergoing curative resection and has been reported to be approximately 30% for endometrial cancer, 20% for colon or gastric cancer, and less than 5% for most other tumor types (9). The rate of MSI appears lower in the metastatic setting, with approximately 5% of colorectal cancers being MSI-H (7, 10).

The prognostic relevance of MSI-H appears to be stage specific. For example, patients with localized, surgically resected MSI-H colorectal cancer appear to have a favorable prognosis compared with MSS colorectal cancer; however, this favorable effect is not maintained in patients with metastatic disease (9).

Clinical Trials

This sBLA included data from 5 clinical trials: KN-012, 028, 016, 158, and 164 (see Table 1; refs. 2, 7). All but one of the patients with mCRC were enrolled in 1 of 2 trials: KN-016, a Johns Hopkins University–sponsored trial that enrolled patients across 6 clinical sites in the United States; and KN-164, a Merck-initiated trial that enrolled patients at 21 clinical sites across 9 countries. Patients with mCRC were eligible for enrollment into KN-016 if they received two or more prior regimens. Patients in KN-164 received prior fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy. Patients with MSI-H/dMMR non-colorectal cancers were prospectively enrolled (KN-016, 158) or retrospectively identified (KN-012, 028, and 158) in 1 of 4 clinical trials. Patients with non-colorectal cancer tumors were eligible for enrollment in these trials if they had received one or more prior regimen for their disease. Studies KN-012, 028, and 158 were Merck-initiated trials; eligibility into Studies KN-012 and KN-028 also required patients to have evidence of PD-L1–positive tumors. Patients in these 5 clinical trials received pembrolizumab at either 10 mg/kg i.v. every 2 weeks or at 200 mg i.v. every 3 weeks for a maximum of 24 months or until unacceptable toxicity or disease progression that was either symptomatic, rapidly progressive, required urgent intervention, or occurred with a decline in performance status. The primary efficacy outcome measure in all trials was ORR according to RECIST 1.1 as assessed by blinded independent central radiologist review.

Table 1. MSI-H/dMMR trials

Clinical trial	Design	*N*	Testing for MSI-H/dMMR	Regimen	Prior therapy
KN-016	– Investigator initiated – Prospective, single-arm – Colorectal cancer and non-colorectal cancer cohorts	28 colorectal cancer 30 non-colorectal cancer	Local PCR or IHC	10 mg/kg every 2 weeks	– Colorectal cancer: ≥2 prior regimens – Non-colorectal cancer: ≥1 prior regimen
KN-164	– Merck initiated – Prospective, single-arm – Patients with colorectal cancer	61	Local PCR or IHC	200 mg every 3 weeks	Prior FP, oxaliplatin, and irinotecan ± anti-VEGF/EGFR biologic
KN-012	– Merck initiated – Patients retrospectively identified as MSI-H/dMMR in a multicohort trial – PD-L1–positive cancers	6[a]	Central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KN-028	– Merck initiated – Patients retrospectively identified as MSI-H/dMMR in a multicohort trial – PD-L1–positive cancers	5[a]	Central PCR	10 mg/kg every 2 weeks	≥1 prior regimen
KN-158	– Merck initiated – Prospective cohort of patients MSI-H/dMMR non-colorectal cancer or – Retrospective identification of MSI-H in patients with 1 of 10 rare tumor types	19[a]	Local PCR or IHC (central PCR for patients in rare tumor non-colorectal cancer cohorts)	200 mg every 3 weeks	≥1 prior regimen
Total		149			

Abbreviation: FP, fluoropyrimidine.
[a]In KN-012, 6 of 96 patients tested identified as MSI-H; in KN-028, 5 of 265 patients tested identified as MSI-H; and in KN-158, 3 of 54 patients retrospectively tested were identified as MSI-H.

Results

Across the 5 clinical studies contributing data to this marketing application, 149 patients were identified with MSI-H/dMMR cancers, consisting of 90 patients with MSI-H/dMMR mCRC and 59 patients with other MSI-H/dMMR cancers (14 different cancer types). Among the 149 patients, the median age was 55 years (36% age 65 or older), 56% were men, and Eastern Cooperative Oncology Group (ECOG) performance status was 0 (36%) or 1 (64%). Most patients were White (77%); however, 19% were Asian and 2% were Black. The median number of prior therapies for metastatic or unresectable disease was two. Eighty-four percent of patients with mCRC and 53% of patients with other solid tumors received two or more prior lines of therapy.

Investigators prospectively determined MSI-H or dMMR tumor status in most patients (135/149) using local laboratory-developed, PCR tests for MSI-H status or IHC tests for dMMR status. Forty-seven patients had dMMR cancer identified by IHC, 60 had MSI-H identified by PCR, and 42 were identified using both tests. Merck retrospectively identified 14 of the 149 patients as MSI-H by testing tumor samples from a total of 415 patients enrolled in KN-012, 028, or 158 using a central laboratory-developed PCR test; across these 415 patients, the incidence of MSI-H or dMMR tumors was 3.4% [95% confidence interval (CI), 1.9–5.6].

There were 59 responders identified from the 149 patients for an ORR of 39.6% (95% CI, 31.7–47.9), with a 7% complete response rate. The duration of response ranged from 1.6+ months to 22.7+ months, with 78% of responses lasting ≥6 months. Because the median duration of follow-up from initiation of treatment was less than one year, the median duration of response could not be estimated (Fig. 2). Conclusions cannot be made regarding response effects across the different trials due to limitations in sample size, differences in study design (Table 1) or differences in eligibility criteria, or patient characteristics. Although KN-016 used a higher dose than KN-164 or KN-158, a retrospective report from a tertiary referral center that administered a 2 mg/kg every 3-week dose (to all but 2 patients) reported a similar response rate as KN-016 (11). There was also no exposure–response relationship observed at the 200 mg dose when patients were assessed by exposure quartiles. The safety profile of pembrolizumab across this population was similar to that described in the Keytruda product labeling.

Regulatory Insights

The FDA approval of pembrolizumab for MSI-H/dMMR cancers represents the first time a drug has been approved based on a common biomarker rather than the primary cancer type. The FDA considered the totality of data, including clinical trial results and supportive scientific data that MSI-H/dMMR tumors are more likely to achieve an immune response leading to tumor shrinkage following pembrolizumab treatment.

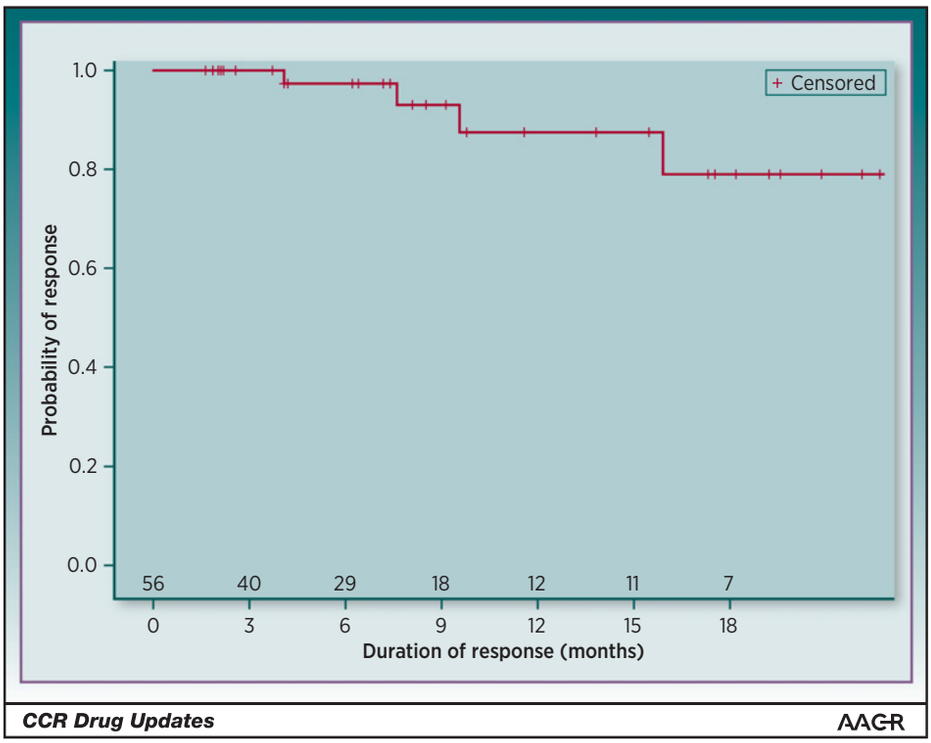

Figure 2.
Kaplan–Meier curve for duration of response.

Pembrolizumab for the treatment of MSI-H tumors, regardless of primary site, was approved under the provisions of accelerated approval based on a demonstration of durable responses. The evidence of efficacy (ORR of 39.6%, complete response rate of 7%, and duration of response of 6 months or longer in 78% of responding patients) is clinically meaningful. The FDA has granted regular approval 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 very durable when the overall benefit–risk profile is favorable (12–15). In this application, however, the possibility of differential activity (ORR and response duration) exists in different tumor types based on extent of prior treatment, disease burden, or other factors. This provides uncertainty regarding the generalizability of clinical benefit across this indication. Therefore, as a condition of this approval, Merck must submit the results of clinical trials that verify and further describe the clinical benefit based on a larger patient experience (124 patients with colorectal cancer; at least 300 patients with non-colorectal cancer, including a sufficient number of patients with prostate cancer, thyroid cancer, small-cell lung cancer; and ovarian cancer; and 25 children) with adequate duration of follow-up (at least 12 months from the onset of response) to characterize response rate and duration. This information may also be supplemented with real-world data in the unexpected scenario where there is a specific tumor type that may be unresponsive to checkpoint inhibition in the presence of MSI-H/dMMR tumor phenotype; such data could also be used to update product labeling.

Although overall survival is a clear measure of clinical benefit, the FDA did not require that randomized trials be conducted to evaluate for effects on overall survival (or progression-free survival) as equipoise may no longer exist. Despite this, Merck has chosen to conduct a randomized trial (KN-177) comparing single-agent pembrolizumab with standard cytotoxic chemotherapy in the first-line treatment of metastatic MSI-H/dMMR colorectal cancer. Because receipt of pembrolizumab is permitted after progression on standard chemotherapy, the trial may be unable to assess whether pembrolizumab improves overall survival.

A concern raised during the review of the application resulted in a requirement to conduct assessment of safety and activity in pediatric patients with central nervous system (CNS) malignancies, given published literature reports of antitumor responses and cerebral edema following checkpoint inhibition (a different PD-1 inhibitor) in pediatric patients with biallelic dMMR primary CNS malignancies (16, 17). On the basis of this concern, the FDA included a limitation of use in product labeling stating that the safety and effectiveness of pembrolizumab in pediatric patients with MSI-H CNS cancers has not been established. The purpose of this postmarketing requirement is to assess the safety of pembrolizumab given the potential risks of increased intracranial pressure arising from an immune response to treatment in the brain (e.g., edema or lymphocytic infiltration).

An additional consideration during the review of the application was the potential absence of accurate and reproducible tests to identify patients with MSI-H/dMMR cancers across health care sites. Although the FDA generally expects that companion *in vitro* diagnostic device(s) will be approved contemporaneously with the drug, FDA guidance (18) states that "if the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device, the FDA does not intend to delay approval of changes to the labeling of the therapeutic product until the IVD companion diagnostic device is approved or cleared." Because accrual of patients was predominantly based on PCR-based tests

for MSI-H and IHC-based tests for dMMR available in the community as laboratory-developed tests and given the efficacy observed, the FDA determined that the risk to patients with "false positive" tumors is low in this setting where no satisfactory alternatives exist, such that approval should not be delayed until a companion diagnostic test is FDA approved for this use. Instead, the FDA and Merck agreed that companion diagnostic tests for detection of MSI-H/dMMR across all cancers may be developed postmarketing as agreed-upon commitments. Although not specifically stated in the commitments, the potential exists for next-generation sequencing technology to identify MSI (19). Because such an approach could facilitate the efficient use of scarce tissue through simultaneous testing for multiple uncommon genetic abnormalities (e.g., mutations in ROS-1, BRAF, TRK), the FDA endorses the development of next-generation sequencing (NGS) and other technology that facilitates personalized medicine.

Although not evaluated in this clinical database, biological reasons may exist for the observed discordance between MSI-H and dMMR results and it is unknown whether these discordances affect response to pembrolizumab. One example involves patients with *POLD* or *E* mutations who may test positive for MSI-H and negative for dMMR. These patients have a very high mutation load that may predict a differential (better) response to pembrolizumab. Conversely, some patients with MSH6 mutations, either germline or due to external causes including prior temozolomide, may not demonstrate MSI (20, 21) and therefore may be less likely to respond to treatment. As additional data become available in either the postmarketing studies or published literature, product labeling may require updating to identify subpopulations of patients with MSI-H or dMMR where the likelihood of response to pembrolizumab differs. Data from at least 124 patients with colorectal cancer enrolled in Merck-initiated trials and at least 300 patients with non-colorectal cancer are expected to be submitted to the agency in March 2023.

The FDA acknowledges that additional unanswered questions exist with regard to use of pembrolizumab in this population. Such questions include the optimal sequence of treatment with immunotherapy compared with standard therapy, what is the optimal duration of therapy, and whether the addition of other drugs to pembrolizumab would improve outcomes. In addition, because MSI identifies patients with high tumor mutation burden (TMB), it is possible that TMB could be useful as a predictor of response to checkpoint inhibitor or perhaps to identify patients with a low probability of response (i.e., whose tumors harbor low TMB). Development of site-agnostic indications requires forethought regarding both the drug and the method of selection of patients (e.g., companion diagnostic device). Furthermore, collaboration between stakeholders (government, industry, academia, patients) will be necessary to define these potential new indications.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): L. Marcus, S.J. Lemery, P. Keegan, R. Pazdur
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