FDA Approval Summary: Accelerated Approval of Pembrolizumab for Second-Line Treatment of Metastatic Melanoma

Meredith K. Chuk1, Jennie T. Chang2, Marc R. Theoret1, Emmanuel Sampene3, Kun He2, Shawna L. Weis1, Whitney S. Helms1, Runyan Jin3, Hongshan Li3, Jingyu Yu3, Hong Zhao3, Liang Zhao4, Mark Paciga5, Deborah Schmiel5, Rashmi Rawat5, Patricia Keegan1, and Richard Pazdur1

Abstract

On September 4, 2014, the FDA approved pembrolizumab (KEYTRUDA; Merck Sharp & Dohme Corp.) with a recommended dose of 2 mg/kg every 3 weeks by intravenous infusion for the treatment of patients with unresectable or metastatic melanoma who have progressed following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Approval was based on demonstration of objective tumor responses with prolonged response durations in 89 patients enrolled in a randomized, multicenter, open-label, dose-finding, and activity-estimating phase 1 trial. The overall response rate (ORR) by blinded independent central review per RECIST v1.1 was 24% (95% confidence interval, 15–34); with 6 months of follow-up, 86% of responses were ongoing. The most common (≥20%) adverse reactions were fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. Immune-mediated adverse reactions included pneumonitis, colitis, hepatitis, hypophysitis, and thyroid disorders. The benefits of the observed ORR with prolonged duration of responses outweighed the risks of immune-mediated adverse reactions in this life-threatening disease and represented an improvement over available therapy. Important regulatory issues in this application were role of durability of response in the evaluation of ORR for accelerated approval, reliance on data from a first-in-human trial, and strategies for dose selection. Clin Cancer Res; 23(19): 5666–70. ©2017 AACR.

Introduction

Historically, patients with metastatic melanoma have had an estimated median overall survival (OS) of less than 1 year (1). Older treatments approved by the FDA include dacarbazine and IL2, which demonstrate low response rates, and for IL2, considerable toxicity. The FDA approved ipilimumab and vemurafenib in 2011 based on improvements in OS over dacarbazine. In 2013, the FDA approved dabrafenib and trametinib as single agents on the basis of improvement in progression-free survival (PFS) over dacarbazine or paclitaxel. At the initial approval of pembrolizumab, these six drugs represented available therapy for patients with advanced melanoma. Patients who progressed following these therapies represented a patient population with an unmet medical need.

Alterations in the immune response have been shown to play a role in the pathogenesis of melanoma. One method of exploiting relevant immune pathways is to block inhibitory signals of T-cell activation to enhance the endogenous antitumoral immune response (2, 3). The programmed death-1 (PD-1) pathway, including PD-1 and its ligands, PD-L1 and PD-L2, functions to maintain self-tolerance, prevents the development of autoimmunity, and protects normal tissues during an infectious/inflammatory response. Interruption of this pathway, which can be upregulated in a variety of tumors, attempts to restore antitumor immune reactivity (4–6).

Pembrolizumab, an anti–PD-1 monoclonal antibody, received FDA’s breakthrough therapy designation in January 2013 for the treatment of patients with unresectable or metastatic melanoma that is refractory to ipilimumab and for the treatment of patients who are ipilimumab-naïve based on data from 85 patients (ipilimumab-naïve, N = 58; refractory to ipilimumab, N = 27) treated with 10 mg/kg of pembrolizumab. The overall response rate (ORR) was 40% (95% confidence interval, 29–51) as assessed by central independent review per RECIST v1.1. Duration of response (DOR) ranged from 0.9 to 7.9 months. Breakthrough therapy designation is given for a drug that is intended to treat a serious condition where there is preliminary clinical evidence that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies. The FDA review of the Biologics License Application (BLA) for pembrolizumab for the
treatment of patients with unresectable or metastatic melanoma who have progressed following treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, which was approved under the provisions of 21 C.F.R., 601, Subpart E (accelerated approval; ref. 7), is summarized below.

Chemistry

Pembrolizumab is an IgG4κ humanized monoclonal antibody that binds to the PD-1 receptor and blocks the interaction with its ligands, PD-L1 and PD-L2. Each heavy chain contains 447 amino acids, and each light chain contains 218 amino acids. There are 32 cysteine residues that form four disulfide linkages as intrachain bonds and 12 intrachain disulfide bonds. The molecular weight of glycosylated pembrolizumab is approximately 149 kDa.

Nonclinical Pharmacology and Toxicology

Pembrolizumab bound to PD-1 in humans and cynomolgus monkeys to a similar extent but did not bind to PD-1 in rodents; therefore, Merck evaluated the potential for antitumor activity of pembrolizumab in a murine tumor model using a surrogate antibody. Pembrolizumab was tested in 4- and 26-week toxicity studies in cynomolgus monkeys. Effects were limited to an increased frequency of alopecia and liquid/unformed feces in treated animals compared with controls, and a diffuse pattern of immune cell infiltration that lacked clear clinical correlates. No evidence of autoimmune disease was observed.

Published data in other animal models raise concerns about the toxicity of pembrolizumab in patients with chronic infections; infection of PD-1-deficient mice with Mycobacterium tuberculosis resulted in a marked decrease in survival compared with similarly infected wild-type animals, which correlated with increases in both bacterial proliferation and florid and destructive inflammatory responses in the lungs of PD-1-deficient animals compared with wild-type controls (8). Because PD-1 inhibition prevents physiologic downregulation of the immune response, the potential risks of an unchecked immune response following vaccination or multiple exposures to other antigens in patients undergoing treatment with pembrolizumab were communicated in the drug label. In addition, Merck was asked to conduct a postmarketing study to characterize the effect of pembrolizumab on the magnitude of the recall immune response in mice.

Clinical Pharmacology

The pharmacokinetics (PK) of pembrolizumab was studied in 479 patients with advanced melanoma or carcinoma at the dose range of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. Based on a population PK analysis, the mean clearance and elimination half-life with percent coefficient of variation (CV%) are 0.22 L/day (28%) and 26 days (24%), respectively. Steady-state concentrations of pembrolizumab were reached by 18 weeks of repeated dosing with an every-3-weeks regimen, and the increase in the systemic exposure was dose proportional with accumulation of 2.1-fold.

No clinically important differences in the clearance of pembrolizumab were found between patients with renal impairment or mild hepatic impairment and those with normal hepatic and renal function. The PK of pembrolizumab was not studied in patients with moderate to severe hepatic impairment.

Clinical Trial Design

Trial MK3475-P001 (P001) was a first-in-human, international, open-label trial consisting of multiple cohorts evaluating the tolerability and preliminary activity of several doses and schedules of pembrolizumab in patients with a variety of advanced solid tumors, as outlined in Table 1. The primary clinical data supporting the FDA’s decision were obtained in the patients enrolled in cohort B2, supported by patients enrolled in cohorts B1 and D. Patients in cohort B2 were randomized (1:1) to receive either 2 or 10 mg/kg of pembrolizumab by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Ipilimumab-refractory was defined as receipt of at least two doses of ipilimumab (minimum 3 mg/kg) and documented disease progression within 24 weeks of the last dose of ipilimumab. Evaluation by irRC used two-dimensional measurements, required confirmation of disease progression 4 to 6 weeks after first detection, and incorporated the measurements of new lesions into the overall tumor burden (9). Patients with BRAF V600 mutation–positive melanoma were also required to have documented disease progression

<table>
<thead>
<tr>
<th>Part</th>
<th>Cohort</th>
<th>Population</th>
<th>MK-3475 dose (mg/kg)</th>
<th>Interval between doses (weeks)</th>
<th>Patients (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
<td>Refractory solid tumors</td>
<td>1, 3, and 10</td>
<td>2&lt;sup&gt;2*&lt;/sup&gt;</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>A1</td>
<td>Refractory solid tumors</td>
<td>10</td>
<td>2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>A2</td>
<td>Refractory solid tumors</td>
<td>2 or 10&lt;sup&gt;h,c&lt;/sup&gt;</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>13</td>
</tr>
<tr>
<td>B</td>
<td>B1</td>
<td>Melanoma (IPI-naive or IPI-treated)</td>
<td>2 or 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2 or 3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>135</td>
</tr>
<tr>
<td></td>
<td>B2</td>
<td>Melanoma (IPI-refractory)</td>
<td>2 or 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>173</td>
</tr>
<tr>
<td></td>
<td>B3</td>
<td>Melanoma (IPI-naive, IPI-treated, or IPI-refractory)</td>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2 or 3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>248</td>
</tr>
<tr>
<td>C</td>
<td>NSCLC</td>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>Melanoma (IPI-naive)</td>
<td>2 or 10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>103</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>F1</td>
<td>NSCLC (no prior treatment)</td>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2 or 3</td>
<td>43&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>F2</td>
<td>NSCLC (previous systemic treatment)</td>
<td>10&lt;sup&gt;h&lt;/sup&gt;</td>
<td>2 or 3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>200&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: IPI, ipilimumab; NSCLC, non–small cell lung cancer.
<sup>2</sup>Dosing interval of 28 days for cycle 1 for PK analysis and 14 days for cycle 2 and beyond.
<sup>2</sup>Randomized.
<sup>2</sup>Three cohorts with separate cycle 1 intrapatient dose titration followed by either 2 or 10 mg/kg every 3 weeks for cycle 2 and beyond.
<sup>2</sup>Enrollment ongoing at the time of the BLA review.
After treatment with a BRAF and/or MEK inhibitor, patients were ineligible if they had any history of severe immune-related toxicity attributed to ipilimumab [defined as any NCI Common Terminology Criteria for Adverse Events (CTCAE) grade 4 toxicity requiring treatment with steroids or grade 3 toxicity requiring steroid treatment (>10 mg/day prednisone or equivalent) for >12 weeks]; a medical condition that required systemic steroids or other immune-suppressive medication; a history of pneumonitis or interstitial lung disease; or an active infection requiring therapy, including HIV or hepatitis B or C. Tumor response assessments were conducted every 9 weeks.

Investigators used irRC to evaluate imaging during the course of the trial, and patients were allowed to remain on treatment if they experienced progressive disease and met the following criteria: no symptoms and signs indicating clinically significant disease progression, decline in Eastern Cooperative Oncology Group (ECOG) Performance Status, or rapid progression of disease or progression, or critical anatomic sites requiring urgent medical intervention. Patients who continued treatment after progressive disease were rescanned after 4 to 6 weeks and discontinued treatment if progressive disease was confirmed.

The primary endpoint of cohort B2 was confirmed ORR as assessed by blinded independent central review (BICR) using RECIST v1.1. With 160 patients, there was approximately 85% power to detect a 15% difference in ORR between doses at a 10% one-sided type I error rate, assuming that the ORR in the inferior arm was 10%. ORR by irRC was evaluated as a secondary endpoint.

### Results

#### Patient characteristics

The baseline demographic and tumor characteristics of the 173 patients treated in cohort B2 were as follows: median age 61 years (range, 18–88); 36% age ≥65; 60% male; 97% White; 66% and 34% with an ECOG Performance Status of 0 and 1, respectively; 17% BRAF V600 mutation; 39% elevated lactate dehydrogenase; 82% M1c disease; 9% brain metastases; and 73% two or more prior therapies for advanced or metastatic disease.

#### Efficacy

The efficacy results for cohort B2 of trial P001 are summarized in Table 2. Pembrolizumab at the 2 mg/kg and 10 mg/kg doses demonstrated ORRs of 23.6% and 23.8%, respectively, according to RECIST v1.1. The median DOR was not reached, but responses ranged from 1.4+ to 8.5+ months (Table 2). Additional cohorts of trial P001 with longer duration of follow-up (at least 1 year and 9 months, respectively, for cohorts B1 and D) were analyzed to provide supportive evidence of the effect on ORR and on the durability of response.

Response rates were similar as assessed by the BICR per RECIST v1.1 and by irRC (Table 3). Only one of the 89 patients receiving pembrolizumab 2 mg/kg every 3 weeks in cohort B2 was found to have progressive disease after 2 weeks.
have new lesions in the context of an overall decrease in tumor burden and was classified as having progressive disease by RECIST but a partial response by irRC.

Safety

The FDA’s review concentrated on patients receiving 2 mg/kg in cohort B2 for description of common adverse events (AE) in product labeling, and on a pooled analysis of the 411 patients with unresectable or metastatic melanoma treated on cohorts B1, B2, and D to identify and characterize immune-related AEs (irAE).

The most common (≥20%) adverse reactions with pembrolizumab administered at 2 mg/kg every 3 weeks were fatigue (47%), cough (30%), pruritus (30%), nausea (30%), rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%), and diarrhea (20%).

The pooled safety population consisted of patients who received pembrolizumab at a dose of either 2 mg/kg every 3 weeks (N = 162), 10 mg/kg every 3 weeks (N = 192), or 10 mg/kg every 2 weeks (N = 57). The median duration of exposure was 6.2 months (range, 1 day–24.6 months), and patients received a median of 10 doses (range, 1–51). The toxicity profile appeared similar across the three dosages. Ten percent of patients discontinued pembrolizumab for AEs, most commonly (0.7%) for pneumonitis. Eighteen percent of patients had treatment delays due to AEs.

The protocol defined irAEs as an AE of unknown etiology associated with drug exposure and consistent with an immune phenomenon where efforts were made to exclude neoplastic, infectious, metabolic, toxin, or other etiologic causes. In the pooled analysis, 23% of patients experienced irAEs (any grade), including 5% with grade 3 to 4 irAEs. Serious irAEs included hypothyroidism (8.3%), pneumonitis (2.9%), hyperthyroidism (1.2%), colitis (1%), nephritis (0.7%), hypophysitis (0.5%), and hepatitis (0.5%). Other irAEs in >1% of patients were rash, vitiligo, pruritus, arthralgia, diarrhea, myalgia, cough, and pyrexia. Clinically significant irAEs in <1% of patients receiving 2 mg/kg in cohort B2 were exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency.

Discussion

The development program for pembrolizumab—the first FDA-approved PD-1–blocking antibody—used three of the four FDA-expedited programs for development and review of drugs for serious and life-threatening diseases (breakthrough therapy designation, priority review, and accelerated approval; ref. 9). Pembrolizumab was the first oncology drug granted breakthrough therapy designation, a program that facilitated frequent interactions with the FDA during development. The BLA for pembrolizumab was designated priority review and received accelerated approval in September 2014 for the treatment of patients with advanced refractory melanoma—less than 4 years from the date of initial Investigational New Drug (IND) submission—based on a favorable benefit-risk profile, with demonstration of a clinically relevant ORR with prolonged DORs and an acceptable toxicity profile in this patient population with an unmet medical need (Table 4).

This expedited development program consisted of data from one randomized cohort of a large "phase 1" trial that had multiple disease-specific, activity-estimating expansion cohorts. Trial P001, a first-in-human trial, was initially designed to enroll 18 patients with refractory solid tumors in a "3 + 3" dose-escalation cohort to determine a maximum tolerable dose, followed by 14 patients with melanoma and renal cell cancer in disease-specific expansion cohorts. Over 2.5 years and eight amendments, Merck expanded the planned accrual to approximately 1,100 patients in nine disease-specific expansion cohorts that explored multiple doses and subpopulations. The evolution of trial P001 has been previously described (11). This trial demonstrates that the nomenclature traditionally assigned to clinical trials at successive stages of development (i.e., phase 1 for dose and toxicity evaluation, phase 2 for activity estimation, and phase 3 for determination of clinical benefit) is not adequate to describe complex, seamless-design clinical trials that, in select circumstances with highly effective drugs, may support regulatory approval. The advantage of this approach is an efficient development program that has the potential to rapidly accrue patients and allow flexibility in exploration of activity. However, given the exposure of large numbers of patients to an unaapproved drug, the conduct of these large trials requires considerable oversight, and consideration must be given to measures that ensure patient safety, appropriate patient selection, adequate informed consent, and adequate justification for sample sizes in expansion cohorts in prespecified statistical designs (11–13).

Although a single trial was used to evaluate antitumor activity, there was an adequate sample size to assess the ORR with
reasonable precision, the ability to make comparisons of the treatment effect with two different dosage regimens, and sufficient safety experience. The major issue was the short duration of follow-up in cohort B2 such that the DOR, which was a major consideration in assessing antitumor activity, was imperfectly characterized.

In addition to the use of a single trial to support regulatory approval, several other important regulatory issues were addressed during the BLA review and included evaluation of a unique AE profile, dose selection, and use of alternative endpoints for immunotherapy drugs. IrAEs are a unique aspect of the safety profile of pembrolizumab. Serious irAEs observed in patients at the time of initial approval included pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyper- and hypothyroidism. These events were managed with steroid treatment and dose delays, and were considered acceptable in patients with a severe and life-threatening disease. A Risk Evaluation and Mitigation Strategy was not considered necessary given the experience of the medical community in managing similar irAEs from ipilimumab.

The doses of pembrolizumab chosen for evaluation in cohort B2 were based upon a PK/pharmacodynamic (PD) approach using clinical biomarker (IL2 release) and a translational PK/PD projection of clinical response based on preclinical studies, as an MTD was not reached in the initial dose-escalation cohorts. The results of these analyses suggested that 1 to 2 mg/kg every 3 weeks was the lowest dose range with a high likelihood of providing substantial clinical benefit. The exposure–response relationship between 2 and 10 mg/kg every 3 weeks was flat for both efficacy (ORR) and safety (immune-related and NCI CTCAE grade 3–5 or serious AEs), supporting the approval of the lower dose (14). Thus, the PK/PD approach toward dose selection was a good model for prediction of treatment effects. This finding underlies the importance of verifying PK/PD modeling through clinical trials and the need to continue to assess and refine optimal dosage regimens through dose-ranging clinical trials, preferably through randomization to doses, as occurred with cohort B2.

The protocol for P001 initially specified that the primary endpoint of cohort B2 was ORR determined by the investigator using irRC but was amended at the request of the FDA, as there are insufficient data with use of irRC to determine whether it provides any advantages over RECIST for evaluating antitumor activity or predicting clinical benefit. The use of RECIST in this trial did not underestimate the clinical activity of pembrolizumab as assessed by ORR compared with irRC; therefore, the role of irRC in assessing antitumor activity remains unclear.

Pembrolizumab was approved under the accelerated approval pathway given the uncertainty of the relationship of the observed ORR and DOR to effects on PFS and OS. Clinical trials designed to verify clinical benefit were required and were ongoing at the time of approval.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Disclaimer
The Deputy Editor handling the peer review and decision-making process for this article has no relevant employment associations to disclose.

Authors’ Contributions
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.T. Chang, R. Pazdur
Writing, review, and/or revision of the manuscript: M.K. Chuk, J.T. Chang, M.R. Theoret, E. Sampene, K. He, S.L. Weiss, W.S. Helms, R. Jin, H. Li, J. Yu, H. Zhao, M. Paciga, D. Schmiel, P. Keegan
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.T. Chang, R. Jin, P. Keegan, R. Pazdur
Study supervision: J.T. Chang, R. Pazdur
Other (I was the primary reviewer for pembrolizumab at time of clinical development, which included reviewing and granting the breakdown designation to pembrolizumab): J.T. Chang
Other (I am one of the product quality reviewer who contributed to the product description in this manuscript and reviewed the manufacturing, chemistry, and control of pembrolizumab in the licensing application): R. Rawat

Received October 12, 2016; revised December 8, 2016; accepted February 20, 2017, published OnlineFirst February 24, 2017.
FDA Approval Summary: Accelerated Approval of Pembrolizumab for Second-Line Treatment of Metastatic Melanoma


Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-16-0663

This article cites 10 articles, 3 of which you can access for free at: http://clincancerres.aacrjournals.org/content/23/19/5666.full#ref-list-1

This article has been cited by 6 HighWire-hosted articles. Access the articles at: http://clincancerres.aacrjournals.org/content/23/19/5666.full#related-urls

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, use this link http://clincancerres.aacrjournals.org/content/23/19/5666. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.