CCR Drug Updates

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FDA Approval Summary: Pembrolizumab for the Treatment of Patients with Unresectable or Metastatic Melanoma

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Abstract

On December 18, 2015, the FDA granted regular approval to pembrolizumab (KEYTRUDA; Merck Sharp & Dohme Corp.) for treatment of patients with unresectable or metastatic melanoma based on results of two randomized, open-label, active-controlled clinical trials. In trial PN006, 834 patients with ipilimumab-naïve metastatic melanoma were randomized (1:1:1) to pembrolizumab 10 mg/kg i.v. every 2 or 3 weeks until disease progression or ipilimumab 3 mg/kg every 3 weeks for up to four doses. In trial PN002, 540 patients with ipilimumab-refractory metastatic melanoma were randomized (1:1:1) to pembrolizumab 2 or 10 mg/kg i.v. every 3 weeks or to investigator's choice of chemotherapy. In trial PN006, patients randomized to pembrolizumab demonstrated a statistically significant improvement in overall survival compared with ipilimumab [every-2-week arm: hazard ratio (HR) = 0.63; 95% confidence interval (CI), 0.47–0.83; $P < 0.001$; every-3-week arm: HR = 0.69; 95% CI, 0.52–0.90; $P = 0.004$]. In both trials, patients receiving pembrolizumab demonstrated statistically significant improvements in progression-free survival. The most common (≥2%) immune-mediated adverse reactions in a pooled safety analysis were hypothyroidism, pneumonitis, and hyperthyroidism. Key considerations for approval were determination of pembrolizumab dose and interpretation of tumor response–based endpoints using RECIST or immune-related RECIST. *Clin Cancer Res; 23(19); 5661–5. ©2017 AACR.*

Introduction

Melanoma is a malignant tumor of the melanocytes that represents less than 5% of all skin cancer diagnoses but results in the most deaths from skin cancer. In the United States, it is estimated that 76,380 new melanoma cases will be diagnosed and 10,130 deaths from melanoma will occur in 2016 (1). Although patients with localized disease have an excellent long-term prognosis, patients with metastatic disease have a median overall survival of less than 1 year.

Pembrolizumab is a mAb that binds to the programmed death 1 (PD-1) receptor and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 (2). The development program for pembrolizumab for this indication received orphan drug designation and was granted breakthrough therapy designation. The FDA granted pembrolizumab accelerated approval in September 2014 based on demonstration of durable response rates in patients with unresectable or metastatic melanoma with disease progression following treatment with ipilimumab and, if indicated, a BRAF inhibitor. As a condition of accelerated approval, the FDA issued a postmarketing requirement for the applicant to conduct a confirmatory, multicenter, randomized trial or trials establishing the superiority of pembrolizumab over standard therapy in adult patients with unresectable or metastatic melanoma who are refractory to ipilimumab or who have not been previously treated with ipilimumab.

This article summarizes the FDA review of the trials submitted to verify the clinical benefit of pembrolizumab, the review issues that were identified, and the basis for regular approval of this new indication for pembrolizumab.

Clinical Pharmacology

Pembrolizumab's pharmacokinetics was studied in 2,195 patients who received doses of 1 to 10 mg/kg every 2 weeks or 2 to 10 mg/kg every 3 weeks. On the basis of population pharmacokinetic analyses in patients with solid tumors assuming a time-stationary clearance model, the geometric mean [% coefficient of variation (CV%)] for clearance, steady-state volume of distribution, and terminal half-life were 202 mL/day (37%), 7.38 L (19%), and 27 days (38%), respectively. Steady-state concentrations of pembrolizumab were reached by 19 weeks of repeated dosing with an every-3-week regimen, and the systemic accumulation was 2.2-fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve (AUC) at steady state of pembrolizumab increased dose proportionally

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in the dose range of 2 to 10 mg/kg every 3 weeks. Clearance of pembrolizumab correlated with body weight; a body weight–based dosing regimen reasonably controlled the exposure variation among patients in the clinical trials. Age (range, 15–94 years), gender, renal impairment, mild hepatic impairment, tumor burden, and race had no clinically important effects on the average clearance of pembrolizumab over time.

In an analysis of data from 1,366 patients with unresectable or metastatic melanoma, a flat exposure–response curve was observed across pembrolizumab dosages of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks. In this analysis, maximal reduction in target lesion size from baseline was analyzed in multiple exposure groups spanning the interval, and there was substantial overlap in the confidence intervals (CI) observed in ipilimumab-naïve and in ipilimumab-treated patients. In addition, the dose–response analyses across efficacy endpoints demonstrated that 2 mg/kg every 3 weeks and 10 mg/kg every 3 weeks showed comparable progression-free survival (PFS), overall survival (OS), and overall response rate (ORR) in the ipilimumab-refractory melanoma patients of trial PN002. A flat exposure–toxicity relationship was observed across the dose range of 1 to 10 mg/kg every 2 or 3 weeks.

Clinical Trials

The results of two randomized, open-label, multicenter, active-controlled clinical trials verified the clinical benefit of pembrolizumab for the treatment of patients with unresectable or metastatic melanoma. In both trials, eligibility was limited to patients ages 18 years or older, patients who had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1, and patients with a histologically confirmed diagnosis of unresectable or metastatic melanoma. In trial PN006, patients who had not received more than one prior systemic therapy and who had not received ipilimumab or other antibodies directed against CTLA-4 or PD-1 were eligible; there was no requirement that patients with BRAF V600E mutation–positive melanoma receive BRAF inhibitor therapy. In trial PN002, eligible patients were required to be refractory to ipilimumab and, if BRAF V600E mutation positive, must have had prior treatment with a BRAF inhibitor. Refractoriness to ipilimumab was defined as receipt of at least two doses of ipilimumab and confirmed progressive disease, defined according to immune-related response criteria (irRC), within 24 weeks of the last dose of ipilimumab, where irRC is defined as at least 25% increase in the sum of the two largest perpendicular diameters of index lesions relative to minimum recorded tumor burden and confirmed by a repeat, consecutive assessment no less than 4 weeks from the date first documented. Exclusion criteria in both studies included autoimmune disease, a medical condition that required immunosuppression, HIV, hepatitis B or hepatitis C infection, uveal melanoma, and active brain metastasis.

In trial PN006, patients were randomly allocated 1:1:1 to receive pembrolizumab at a dose of 10 mg/kg i.v. every 2 or every 3 weeks until disease progression or to ipilimumab 3 mg/kg i.v. every 3 weeks for up to 4 doses. Randomization was stratified by line of therapy (0 vs. 1), ECOG Performance Status (0 vs. 1), and PD-L1 expression [$\geq$1% of tumor cells (positive) vs. <1% of tumor cells (negative)] according to an investigational use only (IUO) assay. In trial PN002, patients were randomized to receive one of two doses of pembrolizumab in a blinded fashion (2 or 10 mg/kg i.v. every 3 weeks) or investigator's choice of chemotherapy from among the following: dacarbazine 1,000 mg/m^2 i.v. every 3 weeks; temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days; carboplatin AUC of 6 i.v. plus paclitaxel 225 mg/m^2 i.v. every 3 weeks for four cycles, then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks; paclitaxel 175 mg/m^2 i.v. every 3 weeks; or carboplatin AUC 5 or 6 i.v. every 3 weeks. Randomization was stratified by ECOG Performance Status (0 vs. 1), lactate dehydrogenase (LDH) levels [normal vs. elevated ($\geq$110% upper limit of normal)], and BRAF V600 mutation status [wild type (WT) or V600E mutation]. In both studies, patients received treatment until disease progression required urgent intervention, occurred with a decline in performance status, became symptomatic or rapidly progressive, or was confirmed at 4 to 6 weeks with repeat imaging.

The co-primary endpoints in both studies were OS and PFS as assessed by a blinded independent review committee (BIRC) using the RECIST v1.1. Secondary endpoints included BIRC-assessed confirmed ORR and duration of response. Tumor assessments were performed at 12 weeks after randomization, then every 6 weeks through week 48, followed by every 12 weeks thereafter. Patients in trial PN002 who experienced progression on investigator's choice of chemotherapy were offered pembrolizumab.

In trial PN006, the primary analysis method for both OS and PFS was a stratified log-rank test, with alpha allocation as follows: overall alpha of 0.005 (one-sided) for PFS with Bonferroni adjustment for each pairwise comparison between a pembrolizumab-containing arm with the ipilimumab arm, and 85% power at an overall alpha of 0.02 (one-sided) for OS with Hochberg procedure to adjust alpha for pairwise comparison (pembrolizumab vs. ipilimumab). In trial PN002, the primary analyses for OS and PFS were stratified log-rank tests, with alpha allocation as follows: a total of 0.005 (one-sided) alpha will be allocated to PFS using 0.0025 (one-sided) for each pembrolizumab arm versus chemotherapy comparison with 88% to 92% power to detect a hazard ratio (HR) of 0.65 for each pairwise comparison; an initial alpha of 0.02 (one-sided) is allocated to OS with Hochberg procedure adjusting for two pembrolizumab arms versus chemotherapy, and a fall-back procedure is used: 0.02 (if none of the PFS hypotheses were rejected), 0.0225 (if exactly one of the PFS hypotheses was rejected), or 0.025 (if both PFS hypotheses were rejected).

Patient Characteristics

A total of 834 patients (277 patients in the pembrolizumab 10 mg/kg every-3-week arm, 279 patients in the pembrolizumab 10 mg/kg every-2-week arm, and 278 patients in the ipilimumab arm) were randomized in trial PN006, and 540 patients (180 patients in the pembrolizumab 2 mg/kg every-3-week arm, 181 patients in the pembrolizumab 10 mg/kg every-3-week arm, and 179 patients in the chemotherapy arm) were randomized in trial PN002. In trials PN006 and PN002, respectively, the baseline demographic and disease characteristics were median ages 62 years (range, 18–89 years) and 62 years (range, 15–89 years), 60% and 61% male, 98% and 98% white, 69% and 55% ECOG Performance Status of 0, 36% and 23% BRAF V600 mutation positive, 65% and 82% M1c stage disease, and 32% and 40% elevated LDH. In trial PN002, the three most common chemotherapy regimens used in the investigator's choice arm were dacarbazine (26%), temozolomide (25%), and carboplatin plus paclitaxel (25%). In trial PN006, 80% were PD-L1 positive, 18%

Table 1. Efficacy of pembrolizumab in patients with unresectable or metastatic melanoma

	Trial PN006			Trial PN002[a]		
	Pembrolizumab 10 mg/kg q3w ($n = 277$)	**Pembrolizumab 10 mg/kg q2w ($n = 279$)**	**IPI ($n = 278$)**	**Pembrolizumab 2 mg/kg q3w ($n = 180$)**	**Pembrolizumab 10 mg/kg q3w ($n = 181$)**	**Chemotherapy[b] ($n = 179$)**
OS[a]						
Number of deaths (%)	92 (33%)	85 (30%)	112 (40%)	73 (41%)	69 (38%)	78 (44%)
HR[c] (95% CI)	0.69 (0.52–0.90)	0.63 (0.47–0.83)	—	0.88 (0.64–1.22)	0.77 (0.56–1.08)	—
P[d]	0.004	<0.001	—	0.46	0.13	—
Median OS, mo (95% CI)	NR	NR	NR	11.4 (10.2–NR)	12.5 (9.7–NR)	11.6 (9.0–16.3)
PFS						
Events (%)	157 (57%)	157 (56%)	188 (68%)	129 (72%)	126 (70%)	155 (87%)
Median PFS, mo (95% CI)	4.1 (2.9–6.9)	5.5 (3.4–6.9)	2.8 (2.8–2.9)	2.9 (2.8–3.8)	2.9 (2.8–4.7)	2.7 (2.5–2.8)
HR (95% CI)	0.58 (0.47–0.72)	0.58 (0.46–0.72)	—	0.57 (0.45–0.73)	0.50 (0.39–0.64)	—
P[d]	<0.001	<0.001	—	<0.001	<0.001	—

Abbreviations: IPI, ipilimumab; mo, months; NR, not reached; q2w, every 2 weeks; q3w, every 3 weeks.

[a]OS analysis for trial PN002 was based on an interim analysis.

[b]Physician's choice of chemotherapy: dacarbazine 1,000 mg/m^2 i.v. every 3 weeks; temozolomide 200 mg/m^2 orally once daily for 5 days every 28 days; carboplatin AUC 6 i.v. plus paclitaxel 225 mg/m^2 i.v. every 3 weeks for four cycles, then carboplatin AUC of 5 plus paclitaxel 175 mg/m^2 every 3 weeks; paclitaxel 175 mg/m^2 i.v. every 3 weeks; or carboplatin AUC 5 or 6 i.v. every 2 weeks.

[c]HR compared with chemotherapy.

[d]Stratified log-rank.

were PD-L1 negative, and 2% had unknown PD-L1 status using the IUO assay. Among patients with BRAF V600–mutant tumors, 139 (46%) were previously treated with a BRAF inhibitor and 66% had no prior systemic therapies.

Efficacy Results

Efficacy results are summarized in Table 1. Both trials demonstrated statistically significant improvements in PFS. Trial PN006 also demonstrated a statistically significant improvement in OS. In trial PN006, pembrolizumab demonstrated an improvement in ORR of 34% in the 10 mg/kg every-2-week arm and 33% in the 10 mg/kg every-3-week arm, respectively, compared with 12% in the ipilimumab arm. The duration of objective response was 1.4+ to 8.1+ months for patients treated with pembrolizumab 10 mg/kg every 2 weeks and 1.4+ to 8.2+ months for patients treated with pembrolizumab 10 mg/kg every 3 weeks. In trial PN002, the confirmed ORR was 21% in the pembrolizumab 2 mg/kg arm, 25% in the pembrolizumab 10 mg/kg arm, and 5% in the chemotherapy arm. At the time of analysis, the proportion of patients who had ongoing responses was 87%, 92%, and 63% for the pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, and chemotherapy arms, respectively.

Exploratory subgroup analyses of trial PN006 were conducted in demographic subgroups and baseline tumor characteristics, including BRAF mutation and PD-L1 expression status. Both OS and PFS tended to favor pembrolizumab for most of subgroups. However, in the PD-L1–negative subgroup, there was no difference for OS and PFS comparing both pembrolizumab doses with ipilimumab. In all analyses, the sample sizes of PD-L1–negative patients were too small to draw definitive conclusions.

Safety Results

Immune-mediated toxicities, defined as adverse reactions due to T-cell activation and proliferation, are known safety concerns with the use of pembrolizumab. An immune-related adverse event (AE) is defined as an AE of unknown etiology, which is consistent with an immune phenomenon and is temporally associated with drug exposure. The risks of pembrolizumab were analyzed using pooled data from three trials given evidence of a flat exposure–toxicity relationship across the dose range of 1 to 10 mg/kg every 2 to 3 weeks; these trials were trials PN001 (open-label, multi-cohort, first-in-human dose-escalation, and activity-estimating trial), PN002, and PN006. A total of 2,117 patients (1,567 with melanoma) received pembrolizumab at 2 mg/kg every 3 weeks ($n = 401$), 10 mg/kg every 3 weeks ($n = 1,056$), or 10 mg/kg every 2 weeks ($n = 660$). No new major safety concerns were identified in this analysis. The most common immune-mediated adverse reactions (imAR) among the 2,117 patients were hypothyroidism (7.8%), pneumonitis (2.7%), and hyperthyroidism (2.9%). imARs typically resolved with the use of systemic high-dose corticosteroids, where the dose, type, and schedule varied depending on the adverse reaction. Similar incidence of AEs occurred among patients <65 and ≥65 years of age. Since FDA approval of pembrolizumab in 2014, other clinically important imARs identified in clinical trials and postmarketing experience were bullous pemphigoid, Guillain–Barre syndrome, myasthenia gravis, vasculitis, hemolytic anemia, and partial seizures. In general, imARs occurred at a similar frequency across all three dosage regimens of pembrolizumab tested in PN002 and PN006. The most common adverse reactions (>20%) were fatigue, rash, constipation, diarrhea, nausea, and decreased appetite. The most common serious adverse reaction was pneumonia, which was reported for 43 patients (2.0%).

Discussion

Key considerations in the FDA review of this application concerned (i) the adequacy of tumor response–based endpoints as determined by conventional response criteria (e.g., RECIST v1.1) to describe the treatment effect of pembrolizumab on the co-primary endpoint of PFS and (ii) the adequacy of the data to support a recommended dose of pembrolizumab that was lower than that evaluated in trial PN006.

Investigators conducting clinical trials in melanoma have expressed concern that conventional tumor response criteria (e.g., RECIST v1.1) may not fully capture the treatment effect of checkpoint inhibitors, such as pembrolizumab, on ORR and PFS (3, 4). Specifically, initial disease progression prior to development of an effective antitumor immune response or enlargement

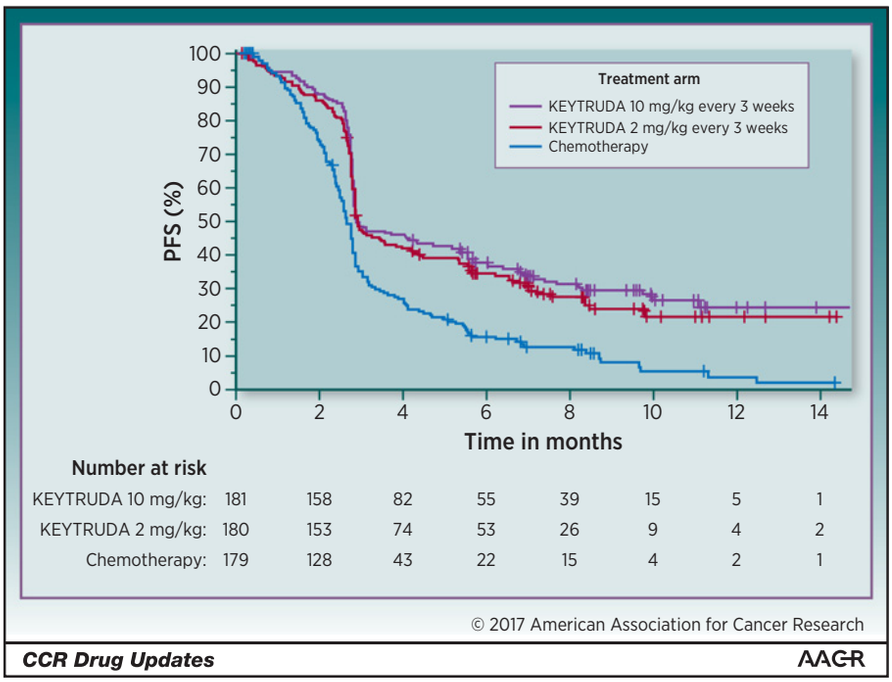

Figure 1.
Kaplan–Meier curve for PFS in trial PN002.

of tumor lesions representative of inflammation rather than tumor growth may result in underestimation of the treatment effect. Efforts were made to capture this treatment effect through use of an alternative response criterion, irRC. The FDA did not analyze PFS based on irRC; however, both RECIST v1.1 and irRC yielded similar ORRs (33.7% vs. 37.3%, respectively, for patients treated with pembrolizumab every 2 weeks; 32.9% vs. 37.5%, respectively, for patients treated with pembrolizumab every 3 weeks; and 11.9% vs. 16.2% for patients treated with ipilimumab).

In addition, any difference in median PFS may not adequately represent the treatment effect on PFS, because this describes effects at a single point and does not characterize effects at all time points. Thus, although the HR representing the entire curve indicated a 43% and 50% reduction in the immediate risks of disease progression or death for the comparison of pembrolizumab 2 mg/kg versus chemotherapy (HR, 0.57) and pembrolizumab 10 mg/kg versus chemotherapy (HR, 0.50), the observed median PFS times for the pembrolizumab arms and the control arm in trial PN002 were similar (see Fig. 1). A *post hoc* and exploratory analysis evaluating the effects on PFS, taking into consideration nonproportional hazard assumptions, is restricted mean PFS time (RMPFST). The RMPFST was 5.4 months (95% CI, 4.7–6.0), 5.8 months (95% CI, 5.1–6.4), and 3.6 months (95% CI, 3.2–3.4) in the pembrolizumab 2 mg/kg, 10 mg/kg, and control arms, respectively. In trial PN006, similar considerations were present for interpretation of the analyses of tumor response–based endpoints, but demonstration of an improvement in OS provided clear evidence of the clinical benefit of pembrolizumab in this setting.

The recommended dose of pembrolizumab proposed by Merck for product labeling was 2 mg/kg i.v. every 3 weeks. Although this dose was not studied in trial PN006, support for this dose is based on a flat exposure–response curve across pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks described above. The FDA review concurred with Merck's proposed recommended dose.

Overall, the efficacy and safety results demonstrated that pembrolizumab has a favorable benefit-to-risk profile in patients with unresectable or metastatic melanoma. The PN006 and PN002 trials demonstrated the clinical benefit of pembrolizumab for patients with metastatic and locally advanced, unresectable melanoma, as evidenced by statistically significant improvements in PFS and, in trial PN006, a statistically significant improvement in OS over standard therapy.

The safety profile of pembrolizumab in patients with unresectable and metastatic melanoma consisted of treatment-emergent imARs affecting multiple organ systems. These adverse reactions were generally managed by supportive measures, including interruption of pembrolizumab dosing and initiation of high-dose, systemic corticosteroids. Uncertainties regarding the risk of pembrolizumab treatment include the occurrence of rare but serious immune-mediated toxicities; a larger population may be required to provide a more complete picture of the toxicity spectrum. Analysis of postmarketing data during the review suggested that the overall safety profile of pembrolizumab is consistent with that described in the labeling information.

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.

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