CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125514Orig1s000

OFFICE DIRECTOR MEMO

Office Director Decisional Memo for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA #	BLA 125514
Applicant Name	Merck
Date of Submission	February 27, 2014
PDUFA Goal Date	October 28, 2014
Proprietary Name / Established (USAN) Name	Keytruda Injection/ pembrolizumab
Dosage Forms / Strength	lyophilized powder/ 50 mg pembrolizumab in single-use vials
Proposed Indication(s)	KEYTRUDA is indicated for the treatment of unresectable or metastatic melanoma in patients who have been previously treated with ipilimumab.
Recommended Action:	*Accelerated Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Patricia Keegan
Regulatory Project Manager Review	Sharon Sickafuse
Medical Officer Review	Jennie Chang & Meredith Chuk
Statistical Review	Emmanuel Sampene
Pharmacology Toxicology Review	Shawna Weis
Quality (OBP) Review	Mark Paciga & Deborah Schmiel
Microbiology Review	Kavlati Suvarna & Reyes Candau-Chacon
Clinical Pharmacology Review	Runyan Jin, Hongshan Li & Jingyu Yu
OPDP	Carole Broadnax
Patient Labeling Team	Sharon Mills
OSI	Lauren Iacono-Connor
CDTL Review	Marc Theoret
OSE/DMEPA	Otto Townsend
OSE/DRISK	Carolyn Yancey
QT-IRT Consult	Justin Earp

OND=Office of New Drugs
OBP=Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Pembrolizumab (also known as MK-3475) is a humanized monoclonal antibody of the IgG4/kappa isotype. Pembrolizumab inhibits the interaction between the programmed cell death-1 receptor (PD-1) and its ligands, programmed death ligand 1 (PD-L1) and PD-L2. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. The proposed mechanism of action of pembrolizumab is inhibition of the PD-1 checkpoint inhibitor by blocking ligand binding and activation. This in turn, results in recognition of self-antigens, leading to autoimmune disorders, and tumor antigens, which are attempting escape immune surveillance.

The trial supporting this application is a single, randomized (1:1), open-label, dose-ranging, multicenter cohort (Cohort B2) within Trial PN001. This sub-study is comprised of 173 patients with advanced or unresectable melanoma, who had progressed on or within 24 weeks of receiving ipilimumab and, if their melanoma tumor was BRAF V600 mutation-positive, had also received a prior BRAF inhibitor, and were randomized and received at least one dose of study treatment. Eighty-nine patients received pembrolizumab 2 mg/kg every 3 weeks (Q3W) and 84 received pembrolizumab 10 mg/kg Q3W.

Pembrolizumab demonstrated a clinically important ORR of 24%, which appears to be durable, and likely to predict a true clinical benefit to patients. The observed adverse reaction profile is notable for treatment-induced autoimmune disorders affecting multiple organ systems; these adverse reactions were managed with suspension of pembrolizumab and initiation of therapeutic, high-dose, corticosteroids. Common adverse reactions of pembrolizumab were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. These common adverse reactions were generally neither severe nor serious (requiring hospitalization or resulting in death).

Due to the serious unmet need of treatment options for the melanoma patient population who have failed standard therapies, the review team decided that Keytruda should be approved earlier than its PDUFA date. However, the pre-approval inspection for the (b) (4) facility, where in-process testing for Keytruda (b) (4) DS is performed, was scheduled for (b) (4), preventing an early action on Keytruda. Keytruda drug substance is manufactured at two sites, (b) (4) and FMC. Therefore, the sponsor decided to withdraw the (b) (4) drug substance and drug product, and (b) (4) testing site, from the pending BLA to allow the Agency to take early action. (b) (4)

2. Background

Cutaneous melanoma, from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2014 there will be 76,100 new cases of melanoma and 9,710 deaths due to melanoma in the United States.[1] While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rate is only 16%.

Available therapy for melanoma

There are seven drugs that have been approved by the FDA for the treatment of metastatic melanoma: vemurafenib, dabrafenib, trametinib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea, which was FDA-approved in the 1970's, is no longer used or recommended in clinical practice guidelines for oncology. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

Commonly used off-label treatments, whose use have also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens,

[1] http://seer.cancer.gov/statfacts/html/melan.html (accessed September 2, 2014)

and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments. All currently used off-label treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

On March 25, 2011, FDA approved Yervoy (ipilimumab) for the treatment of unresectable or metastatic melanoma based on demonstration of improved survival [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months for ipilimumab in the gp100 peptides and gp100 peptides (control), respectively. Approval was also supported by the high level results of Protocol CA 184024, a randomized trial of dacarbazine with or without ipilimumab, in which the high level results also demonstrated an improvement in OS [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

On August 17, 2011, FDA approved Zelboraf (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Approval was based on demonstration of an improvement in OS [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and PFS [HR 0.26 (95% CI: 0.20, 0.33); p <0.0001] for patients in the vemurafenib arm as compared to those receiving dacarbazine.

On May 29, 2013, trametinib was approved for treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. Trametinib was not indicated for treatment of patients who have received prior BRAF-inhibitor therapy. Approval was based on demonstration of an improvement in PFS among patients randomized to receive trametinib as compared to those receiving chemotherapy [HR 0.47 (95% CI: 0.34, 0.65)] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm. The limitation of use was based on lack of antitumor activity (objective tumor responses) in patients with BRAF V600E mutation-positive melanoma who had received a BRAF inhibitor.

On May 29, 2013, dabrafenib was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. This approval was based on an improvement in PFS for dabrafenib as compared to dacarbazine [HR 0.33 (95% CI: 0.20, 0.54), p <0.001] with a median PFS of 5.1 months for dabrafenib and 2.7 months for dacarbazine, respectively. Dabrafenib was also approved with a limitation of use (not indicated for use in patients with wild-type BRAF melanoma) based on the potential risks of tumor promotion.

On January 10, 2014, dabrafenib and trametinib were approved for use in combination for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This approval was based on the demonstration of durable response rate. Improvement in disease-related symptoms or OS has not been demonstrated for these drugs used in combination over either drug used alone.

3. CMC/Biopharmaceutics

There are no outstanding quality issues that preclude approval. The chemistry review team issued an overall acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable or pre-approval inspections for certain facilities were waived based on the compliance history of the firm. One manufacturing sites was withdrawn from the BLA to allow an early action to be taken on this application. Stability testing supports an expiry of 18 months at 2-8 C. See CMC post-marketing commitments in the action letter.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharm/tox issues that preclude approval. The BLA contained results of *in vitro* assessments regarding the proposed mechanism of action, *in vivo* studies in several animal models of infection evaluating possible effects of inhibition of the PD-1 pathway on control of infection, and 1-month and 6-month toxicology studies. Based on the proposed indication in patients with late stage cancer with short life expectancy, a carcinogenicity study was not required. Genotoxicity studies were also not required for this monoclonal antibody. Merck provided literature describing investigations

of the effects of disruption of PD-1 signaling in mouse models of allogeneic pregnancy. Merck showed that inhibition of this signaling pathway, either through administration of an anti-PD-L1 antibody or through genetic disruption, can lead to increases in loss of allogeneic pregnancy, leading to the categorization of this drug under Pregnancy Category D.

The 1-month and 6-month toxicology studies were determined to provide drug exposure reaching or exceeding expected exposures in humans at the recommended dose and ex-vivo studies indicated receptor saturation. Despite this, the pathologic findings were muted, with only observation of monocytic and lymphocytic infiltration of various organs and tissues without overt evidence of organ dysfunction resulting from induction of autoimmunity.

5. Clinical Pharmacology

There are no outstanding clinical pharmacology issues that preclude approval. The recommended dose of pembrolizumab 2 mg/kg administered as an intravenous infusion over 30 minutes every 21 days, is supported by the efficacy data from Cohort B2 of Study PN001, and is reasonably safe and supported by the dose-escalation studies carried out in Cohort A of Study PN001. Selection of the 2 mg/kg dose was based on desired pharmacodynamic effects (interleukin-2 release in a peripheral blood mononuclear assay) and clinical experience. The dosage regimen of 2 mg/kg Q3W provided similar ORR to the dose of 10 mg/kg Q3W, however, continuing investigation of dose optimization is being evaluated in ongoing clinical trials, where preliminary results suggest that a more frequent schedule, may be more efficacious than a Q3W schedule.

The application contained the results of a population pharmacokinetic (PK) analysis from sampling of 476 patients who received pembrolizumab at doses of 1, 3 or 10 mg/kg Q2W or Q3W, assessment of anti-product antibodies from patients enrolled in Cohort B2 and Cohort D who received pembrolizumab at the dose of 2 mg/kg Q2W, and assessment of electrocardiographic effects across 500 patients enrolled in the clinical development program for pembrolizumab.

The population PK mean (95% CI) estimates for time to reach steady state concentrations were 129 (118, 142) days, half-life was 25.8 (23.6, 28.3) days, and volume of distribution at steady-state was 7.66 (7.09, 8.13) L. Based on the population PK analysis, there were no clinically important differences in pembrolizumab exposure based on age, gender, tumor type, tumor burden, mild or moderate renal impairment, or mild hepatic impairment. Since pembrolizumab is a monoclonal antibody that is catabolized into amino acids by general protein degradation process, it is unlikely to have an effect on drug metabolizing enzymes or transporters in terms of inhibition or induction and its clearance is unlikely to be affected by renal or hepatic impairment.

There was no evidence of an exposure-response relationship for either safety or efficacy across the dosage regimes of 2 mg/kg Q3W and 10 mg/kg Q3W, based on data from patients enrolled in Cohort B2. In an exploratory, retrospective assessment of data from Cohort B2, there was no indication that therapeutic corticosteroid treatment abrogated the treatment effect of pembrolizumab.

There was a limited assessment for product immunogenicity, which cannot exclude an incidence of anti-product antibodies (APA) of < 3%. There were no APA detected in 97 patients receiving pembrolizumab 2 mg/kg Q3W.

6. Clinical Microbiology

There are no outstanding sterility issues related to product manufacture that preclude approval.

7. Clinical-Efficacy

The trial (Study PN001) supporting this application is a single, randomized (1:1), open-label, dose-ranging, multicenter cohort (Cohort B2) within a large, multi-stage, multiple cohort dose-finding, activity-estimating, safety and tolerability trial. This sub-study is comprised of 173 patients with advanced or unresectable melanoma, who had progressed on or within 24 weeks of receiving ipilimumab and, if their melanoma tumor was BRAF V600 mutation-positive, had also received a prior

BRAF inhibitor, and were randomized and received at least one dose of study treatment. All patients were required to have evidence of active disease progression at the time of enrollment. Key exclusion criteria included the presence of autoimmune disease, requiring therapeutic corticosteroids (> 10 mg prednisone/day), and severe autoimmune adverse drug reactions with prior ipilimumab therapy. Eighty-nine patients received pembrolizumab 2 mg/kg Q3W as an intravenous infusion and 84 received pembrolizumab 10 mg/kg Q3W. The median age was 61 years (36% age 65 or older); 60% male; 97% White; and 66% and 34% with an ECOG performance status 0 and 1, respectively. Disease characteristics were BRAF V600 mutation (17%), elevated lactate dehydrogenase (39%), M1c (82%), brain metastases (9%), and two or more prior therapies for advanced or metastatic disease (73%).

The primary endpoint was best overall response rate (ORR) by independent central radiologic review and integrated medical oncologist disease assessment based on RECIST 1.1. The key secondary efficacy endpoints included estimation of duration of response, estimation of PFS and OS. Supportive objectives included determination of the best overall response and response duration according to RECIST 1.1 by investigators and determination of best ORR according to immune-mediated response criteria (irRC) by investigators and by the IRC.

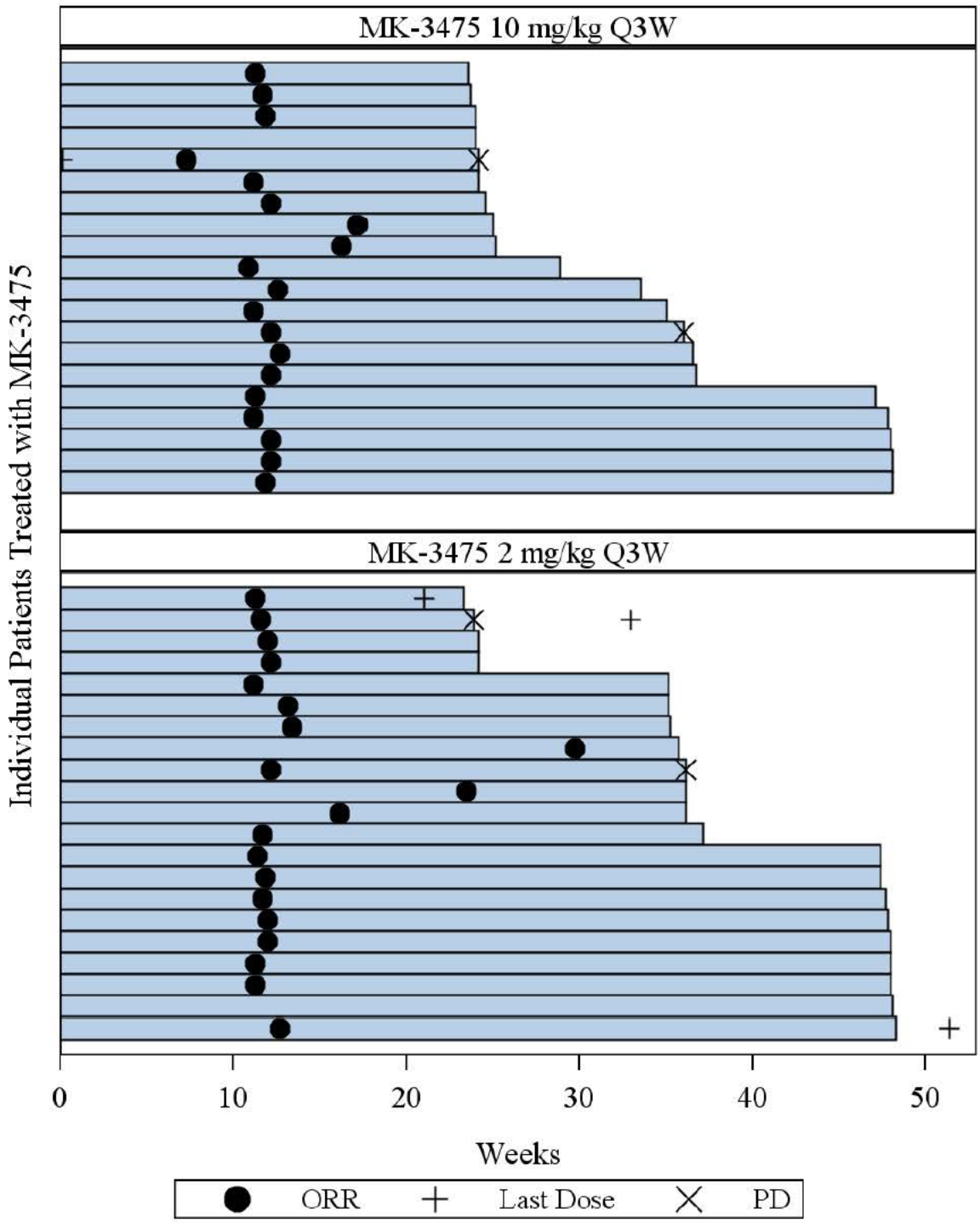
The trial met its primary endpoint of demonstrating an ORR of >10% based on the lower 95% CI around the ORR of 24% (95% CI:15, 34) according to RECIST 1.1 as assessed by blinded IRC. There were one complete response and 20 partial responses identified by the IRC; among the 21 responding patients, three (14%) patients have had progression of disease with durations of response of 2.8, 2.9, and 8.2 months. As of the data cut-off date of October 2013, the remaining 18 patients (86%) have ongoing responses with durations ranging from 1.4+ to 8.5+ months; this includes 8 patients with ongoing responses of 6 months or longer. One additional patient experienced a response according to the WHO immune-related response criteria (IrRC).

Durable objective tumor responses were observed at a similar rate with both treatment regimens. Merck requested approval only for the lower dose administered in Cohort B2. The selection of this regimen as the recommended dose is appropriate since the anti-tumor activity was similar between the two arms in Cohort B with respect to both overall response rate and duration of response.

The results for the primary analysis (ORR by the IRC according to RECIST 1.1) are presented in the table below.

There was an additional single patient in each treatment group who achieved a response according to the immune-related response criteria as determined by the independent review committee, indicating that this type of mixed response is uncommon. In the 2 mg/kg treatment group, the patient with an irRC response developed two new asymptomatic lesions at the first tumor assessment concurrent with a 75% decrease in overall tumor burden; pembrolizumab was continued; with a durable reduction in tumor burden that is ongoing as of the data cut-off (5+ months). The investigator-determined response rate was similar to independently-determined response rate when using RECIST; investigators identified a higher response rate than the independent review committee when using irRC, however the investigators did not use an “as-treated” population, which likely inflated the investigator-determined response rate by irRC (see Statistical Review). The Agency’s experience with this novel response criteria is limited; however these data suggest that ORR based on RECIST and irRC will yield similar results.

Outcome Measure	Pembrolizumab 2 mg/kg Q3W (n=89)	Pembrolizumab 10 mg/kg Q3W (n=84)
Best Overall Response Rate (95% Confidence Interval)	23.6% (15.2; 33.8)	23.8% (15.2; 34.3)
Complete Response Rate	1.2% (n=1)	1.2% (n=1)
Partial Response Rate	22.5% (n=20)	22.6% (n=19)
Median Duration of Response (Range in months)	Not Reached (1.4+; 8.5+)	Not Reached (1.8+, 6.2+)



Database Cutoff Date: 18OCT013
Data Source: [16.4]

In exploratory subgroup analyses, there were no large differences in response rates based on extent of prior therapy (1 vs. >1), age, gender, or performance status. The observed response rates were numerically lower for patients with BRAF V600

mutation-postive melanoma as compared to those whose tumors did not have these mutations, however the response rates observed in those with BRAF mutation-postive melanoma (17% in both the 2 mg/kg and 10 mg/kg treatment groups) indicate sufficient activity to consider that these patients should be included in the indicated population.

Although the number of events are small, there was no suggestion that PFS or OS were different in the two treatment groups.

8. Safety

The safety database contained adverse event information reported in 411 patients with unresectable or metastatic melanoma received who pembrolizumab administered as an intravenous infusion at doses of 2 mg/kg Q3W or 10 mg/kg Q2W or 10 mg/kg Q3W and were enrolled in Cohorts B1, B2, and D of Study PN001. This safety information was supplemented by complete safety information from sequential dose-escalation cohorts from Study PN001 and by the serious and unexpected adverse drug reactions reported in approximately 2000 patients enrolled completed or ongoing clinical trials of pembrolizumab.

Among the 89 patients receiving the "to-be-recommended" dose of pembrolizumab (2 mg/kg Q3W), the most common adverse events (occurring at a per-patient incidence of ≥20%) were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. Across the safety database of 411 patients, the median duration of exposure to pembrolizumab was 6.2 months. Pembrolizumab was discontinued for adverse reactions in 9% of these patients; the most common adverse reactions resulting in discontinuation of pembrolizumab were pneumonitis, renal failure, and pain. The incidence of serious drug adverse reactions was 36%; the most commonly reported serious adverse drug reactions were renal failure, dyspnea, pneumonia, and cellulitis. The most common severe or clinically significant adverse drug reactions were the induction of autoimmune disorders affecting multiple organs and tissues, resulting from the intended mechanism of action of pembrolizumab with "off-target" effects. Across the pooled safety database of 411 patients with melanoma, the most common and clinically significant autoimmune disorders were pneumonitis, hepatitis, colitis, hypophysitis, hyperthyroidism, and hypothyroidism; the most common was pneumonitis occurring in 2.9% of patients. Autoimmune disorders responded in many cases to interruption or termination of pembrolizumab and high-dose corticosteroid therapy. In addition, important adverse reactions include embryofetal toxicity based on non-product specific literature evaluating the role of PD-1 in embryofetal development and the potential increased risks of uncontrolled infection due to immune dysregulation resulting from perturbation of PD-1 pathway.

9. Advisory Committee Meeting

Pembrolizumab was not referred to an advisory committee because the application did not raise significant public health questions for this indication.

10. Pediatrics

Orphan Drug Designation was granted for pembrolizumab on November 19, 2012 for the treatment of Stage IIB - IV malignant melanoma. Therefore, this application is exempt from the requirements of PREA for the approved indication.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval.

- Risk Benefit Assessment
  The indicated patient population has a serious and life-threatening disease with an estimated 5-year survival of 16%, and there are no satisfactory alternative therapies for these patients as they were no longer responding to ipilimumab or BRAF inhibitor therapy and other FDA-approved drugs have lower reported response rates. The data provided in the

BLA demonstrate a clinically important ORR of 24%, which appears to be durable, and likely to predict a true clinical benefit to patients. The observed adverse reaction profile is notable for treatment-induced autoimmune disorders affecting multiple organ systems; these adverse reactions were managed with suspension of pembrolizumab and initiation of therapeutic, high-dose, corticosteroids. The incidence of fatal autoimmune events appears to less than 1%. Common adverse reactions of pembrolizumab were fatigue, cough, rash, pruritus, nausea, decreased appetite, constipation, arthralgia, and diarrhea. These common adverse reactions were generally neither severe nor serious (requiring hospitalization or resulting in death).

The risk-benefit profile was deemed favorable by Drs. Keegan, Theoret, Chang and Chuk, and I concur with their assessment. Furthermore, all review team members recommend approval.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies (REMS):
  DRISK and the clinical review team have concluded that a REMS is not required for this product to ensure safe and effective use, and I concur.

- Recommendation for other Postmarketing Requirements and Commitments: See action letter.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAMY E KIM
09/04/2014

RICHARD PAZDUR
09/04/2014