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APPLICATION NUMBER:

125554Orig1s000

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 125554
Applicant Name	Bristol Myers Squibb
Date of Submission	July 30, 2014
PDUFA Goal Date	March 30, 2015
Proprietary Name / Established (USAN) Name	Opdivo injection/ nivolumab
Dosage Forms / Strength	injection, for intravenous administration/ 40 mg (10 mg/mL) and 100 mg (10 mg/mL) single-use vials
Proposed Indication(s)	OPDIVO (nivolumab) is indicated for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.
Recommended Action:	*Accelerated Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Division Director	Pat Keegan
CDTL Review	Marc Theoret
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Meredith Chuk & Maitreyee Hazarika
Statistical Review	Sirisha Mushti
Pharmacology Toxicology Review	Shawna Weis & Alexander Putman
Quality Review	Joel Welch, Laurie Graham, & Jibril Abdus-Samad
Quality Microbiology Review	Steven Fong
Clinical Pharmacology Review	Xianhua Cao & Hongshan Li
OPDP	Nick Senior
OSI	Lauren Iacono-Connors
OSE/DMEPA	Otto Townsend
OSE/DRISK	Carolyn Yancey
Maternal Health Team	Miriam Dinatale
Patient Labeling Team	Sharon Mills
QT IRT Consult	(b) (4)

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

1. Introduction

On July 30, 2014, Bristol Myers Squibb submitted a Biologics Licensing Application (BLA) for nivolumab based on a trial demonstrating durable objective responses of sufficient magnitude and durability reasonably likely to predict clinical benefit in patients with progressive disease following ipilimumab and in patients with BRAF V600 (b)(4) mutation-positive melanoma, who have had progressive disease following a BRAF tyrosine kinase inhibitor.

Nivolumab is an IgG4 human monoclonal antibody directed against the programmed cell death 1 (PD-1) receptor that is expressed in activated CD4-positive and CD8-positive T cells, natural killer (NK) cells, B cells, and monocytes as well as in some tumor cells and tumor-infiltrating lymphocytes. The interaction of PD-1 with its ligands, PD-L1 and PD-L2, results in down-regulation of T cell responses. The physiologic function of this pathway is to modulate the immune response to prevent immune-mediated tissue destruction.

2. Background

Melanoma is a malignancy arising in melanocytes, most commonly arising in the skin, referred to as cutaneous melanoma. Cutaneous melanoma accounts for 4.6% of all new cases of cancer, with an estimated 76,100 new cases projected in 2014. Prognosis is directly related to stage of disease, with an overall estimated 9,710 deaths due to melanoma in 2014 and 5-year survival rate of 98% overall, reflecting the good prognosis when diagnosed at an early stage and treated with curative resection. However for patients with metastatic disease, which accounts for 4% all cases of melanoma, the 5-year survival drops to 16%.

Available Therapy

There are eight drugs that have been approved by the FDA for the treatment of metastatic melanoma: vemurafenib, dabrafenib, trametinib, ipilimumab, pembrolizumab, 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, 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, Mekinist (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 (not indicated for treatment of patients who have received prior BRAF-inhibitor therapy) 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, Tafinlar (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 received accelerated approval 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.

On September 4, 2014, Keytruda (pembrolizumab) was approved for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. This accelerated approval was based on demonstration of durable objective responses [ORR 24% (95% CI:15, 34)]. The durability of responses were not fully characterized at the time of approval with 86% of responders 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.

3. CMC

There are no issues that preclude approval of this BLA from a CMC perspective. The CMC discipline provided an overall acceptability recommendation of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable or were waived (for drug product) based on acceptable manufacturing history. Stability testing supports an expiry of 24 months at 2° to 8° C.

4. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval from a nonclinical perspective. This BLA contained results of nonclinical in vitro and in vivo pharmacology studies, chronic toxicology studies in cynomolgus monkeys, and enhanced pre- and post-natal development study in cynomolgus monkeys. The safety of the excipient, degradants, and impurity profile is adequately supported.

The nonclinical pharmacology studies confirmed the mechanism of action of nivolumab and of its binding affinity and specificity for PD-1. Nivolumab enhanced immune responsiveness in vitro with increased T-cell proliferation and interferon gamma production compared to an isotype control. This increase in immune responsiveness is supported by studies in PD-1 knockout models. Published literature describing effects of inhibition of PD-1 binding in in vitro assays, knock-out models, and rodent homologue models suggest that nivolumab may impair antimicrobial immune responses resulting in increased mortality from infection. Nivolumab does not mediate antibody-dependent cytotoxicity or complement-mediated cytotoxicity.

Binding of nivolumab to PD-1 in humans and cynomolgus monkeys blocked binding of PD-1 binding to the receptor; this was not observed with nivolumab administration in rodents or rabbits. Although functional activity was demonstrated in cynomolgus monkeys, 4-week and 13-week repeat dose toxicology studies underestimated the toxicity of nivolumab in human, with histopathology findings limited to inflammatory infiltration in multiple organs but no clinical evidence of immune-mediated toxicity.

In pre-natal studies in cynomolgus monkeys, the incidence of fetal loss in the first and third trimester was higher for nivolumab-treated monkeys at exposures of 9-fold and 42-fold above that achieved in humans at the recommended dose (3 mg/kg every two weeks), as compared to concurrent or historical controls. Fetal malformations were not observed in live births or spontaneous abortions. Among surviving infants of nivolumab-treated dams, there were no clear effects of prenatal nivolumab exposure on neurobehavioral, or clinical pathology parameters throughout the postnatal observation period and no gross or histopathology findings at scheduled termination. Pre-natal exposure to nivolumab did not appear to prevent either T-cell or B-cell responses to immune challenges although enhanced responsiveness may have been present.

5. Clinical Pharmacology

There are no issues that preclude approval from the clinical pharmacology perspective. The following is an excerpt from the clinical pharmacology review:

Efficacy, safety, pharmacokinetic (PK), and immunogenicity data for this application are based on multiple clinical studies with nivolumab administered over the dose range of 0.1-20 mg/kg, where study CA209037 supports the marketing application of nivolumab with 3 mg/kg every 2 weeks (Q2W) dosing regimen. The major findings of the clinical pharmacology review are listed below.

- *The apparent flat exposure-response (E-R) relationship for both efficacy and safety supports the use of the 3 mg/kg Q2W dosing regimen for the indicated patient population.*
- *Treatment emergent anti-nivolumab antibodies were detected in 24 of the 281 evaluable patients (8.5%) who received nivolumab of 3 mg/kg Q2W using an electrochemiluminescence (ECL) based assay. Neutralizing antibodies were detected in two patients (0.7%).*
- *Population PK analyses suggested that age, gender, race, baseline LDH, PD-L1 expression, anti-nivolumab antibody formation, tumor type, and tumor size did not have clinically meaningful effects on the exposure of nivolumab.*

Pharmacokinetics: Based on data from 909 patients who received 0.1-20 mg/kg of nivolumab as a single or multiple doses every 2 or 3 weeks, the population PK mean (CV%) estimates are as follows:

- *Clearance, 9.5 mL/h (49.7%)*
- *Volume of distribution at steady-state, 8.0 L (30.4%)*
- *Half-life, 26.7 days (101%)*
- *Time to reach steady state concentrations of nivolumab, 12 weeks after 3 mg/kg Q2W and the systemic accumulation, approximately 3-fold.*

Patients with moderate or severe hepatic impairment were not included in clinical studies contributing to the population PK analyses. Dedicated hepatic impairment studies were not required since nivolumab is not metabolized by the liver.

A dedicated substudy assessing effects of nivolumab on the QT interval was conducted. This randomized, double-blind, dose-ranging study evaluated nivolumab at doses of 0.3, 2.0, and 10.0 mg/kg administered every 3 weeks in patients with renal cell carcinoma. In this substudy, there was no evidence of clinically important effects of nivolumab on cardiac electrophysiology, including QT interval.

6. Clinical Microbiology

Not applicable.

7. Clinical-Efficacy

The efficacy data supporting this application are from an interim analysis estimating the overall response rate (of one of two co-primary endpoints) in a single arm ongoing trial, Protocol CA209037. Protocol CA209037 is an open-label, randomized (2:1), multicenter, multinational clinical trial designed to demonstrate superior overall response rates and OS (co-primary endpoints) for patients randomized to receive nivolumab 3 mg/kg every 2 weeks as compared to chemotherapy (dacarbazine or carboplatin plus paclitaxel).

On February 13, 2014, BMS proposed to modify the design of Study CA209037 to incorporate a new analysis of ORR; in this new analysis, BMS proposed to calculate the IRRC-assessed ORR in the first 120 patients treated with nivolumab to seek accelerated approval.

Trial Design

The trial supporting this application is Protocol CA 209037, entitled "A randomized, open-label phase 3 trial of BMS-936558 (nivolumab) versus investigator's choice in advanced (unresectable or metastatic) melanoma patients progressing post anti-CTLA-4 Therapy". The trial enrolled 631 patients in 14 countries. Of these, 405 patients were eligible for randomization (272 patients to nivolumab and 133 patients to investigator's choice of chemotherapy).

The efficacy population for the interim analysis of ORR consists of the first 120 patients who were randomized and completed at least 6 months of follow-up in the nivolumab arm or had disease progression or died prior to 6 months of follow-up. Among these 120 patients, the median age was 58 years (range: 25-88), 65% of patients were male, 98% were white, and the ECOG PS was 0 (58%) or 1 (42%). With regard to prognostic characteristics, 76% of the study population had M1c disease, 22% had BRAF V600 mutation-positive melanoma, 56% had elevated LDH at baseline, 18% had a history of brain metastases, and all patients received ipilimumab with more than two-thirds (68%) having received two or more prior systemic therapies for metastatic disease.

The overall response rate was 32% (95% CI: 23, 41) with 4 complete responses and 34 partial responses. Of 38 patients with responses, 33 patients (87%) had ongoing responses with durations ranging from 2.6+ to 10+ months. There were 13 patients with ongoing responses of at least 6 months duration. The objective response rate was 34% (95% CI: 25, 45) in patients with BRAF wild-type melanoma and 23% (95% CI: 9, 44) in patients with BRAF V600 mutation-positive melanoma. Responses appeared to be higher among patients with PD-L1 positive melanoma [ORR 44% (95% CI: 30, 58)] as compared to those with negative or indeterminate findings [22% (95% CI: 12, 34)]. These differences may be due to small numbers rather than true treatment differences--additional data are needed. In addition, responses were seen in all demographic subgroups, based on prior ipilimumab response, ECOG PS, age, gender, region, race, and baseline LDH.

8. Safety

The safety database consisted of 268 patients who received at least one dose of nivolumab 3 mg/kg every 2 weeks and 102 patients who received at least one dose of either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin (AUC 6) dosed every 3 weeks plus paclitaxel 175 mg/m^2 every 3 weeks. The median duration of exposure was 5.3 months in nivolumab-treated patients and 2 months in chemotherapy-treated patients.

The most serious, including fatal, adverse reactions of nivolumab are investigator-determined, autoimmune-mediated organ toxicity, most commonly involving the lungs (3.4% overall; 0.7% fatal pneumonitis), colon (2.2%), liver (1.1%), kidneys (0.7%), and endocrine glands, most often resulting in hypothyroidism (8%) or hyperthyroidism (3%). Other autoimmune-mediated toxicity identified as serious adverse events across the clinical trial experience, which includes ongoing trials (thus precluding a determination of incidence) are hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barre syndrome, and myasthenic syndrome.

The most common Grade 3 or 4 adverse reactions or laboratory abnormalities occurring in 20% of nivolumab-treated patients were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. The most common adverse reactions of nivolumab (defined as ≥ 5% absolute increase in overall incidence over the chemotherapy-

treated group) events over the chemotherapy-treated group) were rash (21% vs. 7%), pruritus (19% vs. 3.9), cough (17% vs. 6%), upper respiratory infection (11% vs. 2%), and edema (10% vs. 5%).

9. Advisory Committee Meeting

This BLA was not referred to the Oncologic Drugs Advisory Committee (ODAC) because this biologic is not the first in its class, the clinical study design was acceptable, and the application did not raise significant safety or efficacy issues that required the advice of the ODAC.

10. Pediatrics

Nivolumab was granted orphan drug designation on January 23, 2013 for the treatment of Stage IIb to IV melanoma and therefore this application is exempt from Pediatric Research Equity Act (PREA) requirements.

11. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Accelerated Approval.

- Risk Benefit Assessment

  Nivolumab demonstrated an overall response rate of 32% which was durable for more than 6 months in approximately one-third of patients. This is approximately two-fold higher than the reported response rates for approved or off-label chemotherapeutic agents and the duration of responses are substantially longer with nivolumab. The toxicity profile of nivolumab includes the serious risks of autoimmune-mediated organ toxicity, which can be fatal, and requires treatment with high-dose corticosteroids. Other than the autoimmune-mediated toxicities, other adverse reactions of nivolumab include rash (21% vs. 7%), pruritus (19% vs. 3.9), cough (17% vs. 6%), upper respiratory infection (11% vs. 2%), and edema (10% vs. 5%).

  Cutaneous melanoma accounts for 4.6% of all new cases of cancer, with an estimated 76,100 new cases projected in 2014. For patients with metastatic disease, which accounts for 4% all cases of melanoma, the 5-year survival drops to 16%. While several drugs have been approved for the treatment of metastatic melanoma in the past three years, the population enrolled in Study CA209037 has received and progressed on these agents and had no satisfactory alternative therapy. The observed response rate of 32%, combined with the durability of the response, is reasonably likely to predict prolongation in PFS of a clinically important magnitude and potentially an improvement in OS. In light of these benefits, the serious autoimmune-mediated organ toxicities of nivolumab are considered acceptable by the medical community and patients in light of the life-threatening nature of relapsed/refractory metastatic melanoma. These toxicities are similar in nature to other recently approved drugs (ipilimumab and pembrolizumab) for treatment of metastatic melanoma and appear to be manageable in most patients (i.e., with high dose corticosteroids).

  The risk-benefit profile was also discussed in the reviews of Drs. Keegan, Theoret, Chuk and Hazarika. All review disciplines recommend approval of this BLA, and I concur with this recommendation.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  None.

- Recommendation for other Post-marketing Requirements and Commitments
  See action letter.

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/s/

TAMY E KIM
12/21/2014

RICHARD PAZDUR
12/21/2014