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APPLICATION NUMBER:

125554Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	December 19, 2014
From	Patricia Keegan
Subject	Division Director Summary Review
BLA #	STN BL 125554/0
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:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
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	Dinko Rekic

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

Division Director Summary Review

1. Introduction

I recommend that this application be approved under the provisions of 21 CFR 601 Subpart E with the agreed-upon labeling, post-marketing requirements and commitments. All scientific review disciplines have recommended approval. The applicant (Bristol Myers Squibb) seeks accelerated approval (under 21 CFR 601 Subpart E) for Opdivo (nivolumab) injection, based on demonstration of durable objective responses of sufficient magnitude and durability that it is reasonably likely to predict clinical benefit in patients with progressive disease following ipilimumab, and for those with BRAF V600(b)(4) mutation-positive melanoma, have also had progressive disease following a BRAF tyrosine kinase inhibitor. The indicated population has a serious, life-threatening disease and no satisfactory alternative therapy.

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.

This BLA relied on the results of an interim, non-comparative analysis of an ongoing, randomized (2:1), open-label study (Protocol CA209037) conducted in patients with metastatic or locally advanced, unresectable melanoma that has progressed following ipilimumab and, if BRAF V600-mutation positive has also progressed following treatment with a BRAF inhibitor. The interim analysis was conducted in the first 120 patients randomized to receive nivolumab 3 mg/kg every two weeks who had completed six months of follow-up from study initiation or had progressed prior to 6 months. Key exclusion criteria included the presence of autoimmune disease, requiring for therapeutic corticosteroids (> 10 mg prednisone/day), and severe autoimmune adverse drug reactions with prior ipilimumab therapy.

The trial met the criteria for the interim analysis, ruling out an overall response rate (ORR) of less than 15%, based on the lower bound of the 95% confidence interval, according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (IRC). In this interim analysis, an objective response rate of 31.7% was observed, with 4 complete responses and 34 partial responses observed. The durability of these responses is uncertain, with 33 of the 38 responding patients (87%) having ongoing responses ranging from 2.6+ to 10+ months; of these, 13 patients had ongoing responses of more than 6 months duration.

Comparative safety data was provided only for Study CA209307. 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 received either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 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 was 2 months in chemotherapy-treated patients. As noted above, the adverse

reaction profile with long-term exposure was not adequately characterized with data limited to only 64 (24%) patients who received nivolumab for more than 6 months and 8 (3%) patients who received nivolumab for more than 1 year.

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%)
Issues considered during this review were

- Whether the observed response rate and response duration were reasonably likely to predict clinical benefit
- Whether the benefits outweighed the risks
- Whether a REMS was required to ensure safe and effective use of nivolumab for the indicated population

2. Background

Indication
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 US 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 ipilimumab (Yervoy, Bristol Myers Squibb) 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 overall survival [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, vemurafenib (ZELBORAF, Genentech Inc.), an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved 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 a statistically significant improvement in overall survival [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and progression-free survival [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 a statistically significant improvement in the progression-free survival 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, 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 a statistically significant and clinically meaningful 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 overall survival has not been demonstrated for these drugs used in combination over either drug used alone.

On September4, 2014, 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)] according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) as assessed by blinded independent central review (IRC). 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.

Regulatory History of the Clinical Development Program

July 28, 2006: IND 100052, sponsored by Medarex, for nivolumab (referred to as MDX-1106) for clinical investigations in patients with recurrent or treatment-refractory non-small cell lung cancer, colorectal adenocarcinoma, malignant melanoma, renal cell carcinoma, and (b) (4) was allowed to proceed. The IND-enabling protocol was a first-in-human, open-label, single dose, sequential dose-escalation study, with an option for multiple doses, every 4 weeks, beginning study week 13.

January 27, 2010: The sponsorship of IND 100052 was transferred to Bristol Myers Squibb.

June 13, 2012: IND 115195 submitted for the clinical development program for the treatment of melanoma, as a result of the splitting of IND 100052 was split into three INDs for disease-specific drug development program: IND 100052 for non-small cell lung cancer; IND 113463 for renal cell carcinoma; and IND 115195 for melanoma.

July 17, 2012: EOP1/pre-Phase 3 meeting held to discuss the development program supporting accelerated approval and verification of clinical benefit. The clinical development program in melanoma consisted of an ongoing dose-escalation and activity-estimating trial (CA209003) conducted under IND 100052; additional pharmacologic activity studies (CA209006, CA209007, CA209004 and CA 209038); and a proposed hypothesis-testing, pivotal study (CA209037), to be conducted under IND 115195. Studies CA209006, CA209007, CA209004 and CA 209038 were designed to explore PD-L1 expression as a potential predictive biomarker for nivolumab in melanoma; BMS described co-development of a PD-L1 IHC assay with DAKO.

Regarding the design of Study CA209037, FDA informed BMS that the proposed study design, eligibility criteria, control arm, and co-primary endpoints were acceptable. FDA stated an accelerated approval of nivolumab based primarily on the interim results of study CA209037 would require demonstration of a robust effect on ORR that was of sufficient magnitude and duration to be reasonably likely to predict clinical benefit and permit a positive risk-benefit determination, This determination would consider available therapies for the

proposed patient population at the time of a marketing application as described in 21 CFR 312.84.

October 4, 2012: Fast track designation granted for treatment of patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.

October 17, 2012: Study CA209037 submitted to IND 115195

January 23, 2013: Orphan drug designation granted for treatment of Stage IIb to IV melanoma.

March 27, 2013: FDA issued an Advice/Information Request letter, advising BMS to:

- Revise protocol to require that primary analysis of ORR be based on independent review and require confirmation of durability for ≥ 4 weeks
- Revise the protocol to require that the investigator select the choice of chemotherapy that will be administered if patient is randomized to the chemotherapy arm
- Systematically collect information on BRAF V600 mutation test method and result: if possible, determine BRAF mutation status at a central laboratory
- Ensure that the statistical analytical plan includes censoring rules and sensitivity analyses for patients who experience symptomatic deterioration in the absence of objective radiographic evidence of disease progression.
- To specify that the significance level for the OS interim analysis to be conducted at the ORR analysis follow O'Brien Fleming alpha spending function
- Revise the protocol to include detailed description of the testing procedures for PFS.

October 3, 2013: Type C meeting held between FDA and BMS, conducted under IND 104225, to discuss the planned global registration strategy for nivolumab. FDA requested that BMS submit a formal proposal for the plan to "decouple" the timing of the analysis of the co-primary endpoints of objective response rate (ORR) and overall survival (OS) in Study CA209037.

October 25, 2013: submission of amendment to IND 115195 requesting FDA's assessment of BMS' proposal to accelerate the timing for submission of an NDA for nivolumab for the treatment of metastatic melanoma following disease progression on ipilimumab treatment.

January 16, 2014: FDA issued an Advice/Information Request letter regarding the proposed modification to the trial to "decouple" the analysis of the co-primary endpoints. FDA stated that

- the proposal to perform an earlier analysis of ORR was acceptable, however FDA disagreed with the proposed change in alpha allocation to the co-primary endpoints and recommended that the two-sided, alpha allocation ratio remains 0.01 for ORR and 0.04 for OS, respectively, as in the original statistical analysis plan;
- ORR based on IRC-determined responses will be considered the primary efficacy endpoint to support a regulatory action; and
- The proposal to include unconfirmed tumor responses as objective responses in the determination of ORR was not acceptable and that as stated in the March 27, 2013

letter "Objective tumor responses will require confirmation at a repeat assessment to verify a minimum durability of tumor responses".

March 17, 2014: FDA issued an Advice/Information Request letter providing the following advice to BMS on the February 13, 2014, amendment containing a revised proposal to modifications to the primary analysis of ORR

- FDA agreed that the proposed plan to analyze confirmed ORR based on independent review in 120 nivolumab-treated patients, with the goal of excluding an overall response rate of less than 15% (based on the lower 95% confidence interval) was acceptable.
- The analysis of ORR should be provided as descriptive statistics only in proposed product and promotional labeling, i.e., no p-value assigned to this analysis.
- The observed response rate that would be considered reasonably likely to predict an effect on overall survival, in support of a request for accelerated approval would consider the magnitude of the confirmed ORR, the durability of the confirmed objective responses, and the risks of treatment.
- The proposed plan of using an overall alpha of 0.04 for the analysis of OS was acceptable.

Regulatory History of BLA

July 30, 2014: BLA 125554 was submitted by Bristol Myers Squibb and received by FDA.

August 27, 2014: Request for proprietary name review submitted to BLA.

October 28, 2014: Submission of 90-day safety update containing new adverse event information in Study CA209037 between the database lock of April 30, 2014 and July 29, 2014 and a listing or brief summary of new suspected and unexpected serious adverse events across all clinical trials.

3. CMC

I concur with the conclusions reached by the quality reviewer regarding the acceptability 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. There are no outstanding issues that preclude approval.

Nivolumab is a human IgG4 monoclonal antibody consisting of (b) (4) (b) (4) It binds to human PD-1and blocks interaction of PD-1 to its ligands, PD-L1 and PD-L2. Nivolumab is produced by (b) (4) (b) (4) The drug substance is formulated at (b) (4) sodium citrate, (b) (4) sodium chloride, (b) (4) mannitol, (b) (4) pentetic acid, and (b) (4) polysorbate 80, at pH 6.0. The drug product, Opdivo, is supplied at concentrations of 10 mg/mL in single dose vials in strengths of 100 mg and 40 mg. The two presentations differ only in fill volume.

The quality review team requested four post-marketing commitments, summarized below, to further assess and improve product characterization.

- BMS agreed to develop a process-specific [redacted] (b) (4) to detect host cell [redacted] (b) (4) proteins in the drug substance. While DS release specifications approved under the BLA are sufficient to ensure adequate quality and safety of nivolumab for the initial marketed product, the commitment to improve and implement a process-specific HCP assay will provide better control of HCP levels in DS.

- BMS agreed to optimize and revalidate the non-reduced CE-SDS method to improve reproducibility. While the approved assay is sufficient to ensure adequate control and safety of nivolumab for the initial marketed product, an improved assay would provide more accurate control of purity in both drug substance and drug product.

- BMS agreed to re-evaluate nivolumab drug substance lot release and stability specifications after 30 lots have been manufactured at the commercial scale and t0 provide the corresponding data, the analysis and statistical plan used to evaluate specifications, with any proposed changes to the specifications, in a final study report.

- BMS agreed to re-evaluate nivolumab drug product lot release and stability specifications after 30 lots have been manufactured at the commercial scale and to provide the corresponding data, the analysis and statistical plan used to evaluate the specifications, with any proposed changes to the specifications, in a final study report.

- BMS agreed to re-evaluate and tighten the endotoxin limits for the following in-process samples: [redacted] (b) (4)

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

The BLA contained the 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 an in vitro (mixed lymphocyte reaction assay) 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 human 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/Biopharmaceutics

I concur with the conclusions reached by the clinical pharmacology and biopharmaceutics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The selection of the dose used in the major efficacy trial, Study CA209037, was based on a dose-finding, safety and tolerability trial, Study CA209003, evaluated nivolumab doses of 0.1, 0.3, 1.0, 3.0, and 10 mg/kg intravenously every 2 weeks in 306 patients with various solid tumors, including 107 patients with melanoma. As noted in clinical pharmacology review, this dose is supported by the population pharmacokinetic analysis and exposure-response and exposure-toxicity relationships.

Characterization of the pharmacokinetic profile of nivolumab is based on the results of a population pharmacokinetic (PK) analysis that included PK data collected from 909 patients with various malignancies enrolled across multiple trials. These trials employed nivolumab doses ranging from who received 0.1 to 20 mg/kg either as a single dose or as multiple doses administered intravenously every 2 or 3 weeks. The exposure to nivolumab increased dose proportionally over nivolumab doses of 0.1 to 10 mg/kg administered every 2 weeks. Based on the population PK analysis, the mean elimination half-life ($t_{1/2}$) of nivolumab is 26.7 days with steady-state concentrations reached by 12 weeks when nivolumab was administered at a dose of 3 mg/kg every two weeks. There was no evidence that age, gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, or mild hepatic impairment had clinically important effects on the clearance of nivolumab. While patients with moderate or severe hepatic impairment, as defined by Child's Pugh class, were not included in clinical

studies contributing to the population PK analyses, dedicated hepatic impairment studies were not required since nivolumab, as an immunoglobulin, is not metabolized by the liver.

In standard exploratory analyses, there was no apparent relationship between nivolumab exposure (based on trough levels following the first dose) and overall response rate. In addition, there was no apparent relationship between nivolumab exposure (based on steady state concentrations) and the incidence of Grade 3 or 4 adverse reactions.

The development of anti-nivolumab binding antibodies was identified in 8.5% of the 281 patients who received nivolumab 3 mg/kg every 2 weeks and were evaluated using a sensitive assay. Of these 281 patients, 0.7% (two patients) developed neutralizing antibodies. Development of binding antibodies did not alter the pharmacokinetics of nivolumab and did not appear to result in increased risks of adverse reactions.
A dedicated substudy assessing for effects of nivolumab on the QT interval was conducted as part of Study 209010. 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/Statistical-Efficacy

The efficacy data provided in this application provide the minimal evidence necessary to assess objective durable responses at the proposed dose and schedule in the indicated population. There was insufficient data to determine whether the dose is optimal, as objective tumor responses have been observed across multiple dose levels (0.3, 1.0, and 3.0 mg/kg) across the clinical development program and the confidence intervals for the observed treatment effect are sufficiently wide to include response rates as low as 23%.

With regard to the major efficacy analysis, three clinical sites, chosen based on the number of patients enrolled and observed overall response rates at these sites, as well as the sponsor and independent review committee site were inspected by FDA. Based on these inspections, the data are deemed reliable.

Key Amendments to Protocol CA209037

The efficacy data supporting this application are derived from interim analysis estimating the overall response rate (of one of the two co-primary endpoints) in a single arm of an 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 overall survival (co-primary endpoints) for patients randomized to receive nivolumab 3 mg/kg every 2 weeks as compared to chemotherapy (dacarbazine or carboplatin plus paclitaxel)

In a February 13, 2014, submission, BMS proposed to modify the design of Study CA209037 to incorporate a new analysis of ORR; in this new analysis, you propose to calculate the IRRC-assessed ORR in the first 120 patients treated with nivolumab to seek accelerated approval. The timing of this analysis will be based on a minimum of 6 months follow-up for all patients and the supporting assumptions are that a minimum of 22 responses out of 120 treated subjects (≥ 18% ORR) would need to be observed for the 99% confidence interval to rule out an ORR <10% based on the lower bound of the 99% confidence interval. An alternative hypothesis is that a minimum of 30 responses (≥ 25% ORR) would need to be observed to rule out an ORR of <15% based on the lower bound of the 99% confidence interval.

Trial Design
Protocol CA 209037, titled "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"

Study design: Open-label, multicenter, multinational, randomized (2:1) trial

Key eligibility criteria: Patients were required to have evidence of progression of disease on or following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The trial excluded patients with autoimmune disease, medical conditions requiring systemic immunosuppression, ocular melanoma, active brain metastasis, or a history of Grade 4 ipilimumab-related adverse reactions (except for endocrinopathies) or Grade 3 ipilimumab-related adverse reactions that had not resolved or were inadequately controlled within 12 weeks of the initiating event.

Treatment plan:
- Arm 1: nivolumab 3 mg/kg as a 60 minute intravenous infusion every 2 weeks until disease progression, unacceptable toxicity, or
- Arm 2: Investigator's choice of chemotherapy defined as either
  - dacarbazine 1000 mg/m^2 intravenously every 3 weeks or
  - carboplatin AUC 6 intravenously on day 1 and paclitaxel 175 mg/m^2 intravenously on day 1 of each 21-day cycle. Tumor assessments were conducted 9 weeks after randomization then every 6 weeks for the first year, and every 12 weeks thereafter.

Randomization (2: 1) was stratified by PD-L1 status ( ), BRAF V600 mutation status 9wild-type vs. mutation-positive), and best response to ipilimumab (complete or partial response or stable disease vs. progressive disease).

Statistical analysis plan: The proposed sample size of 390 patients, considering the 2:1 randomization (nivolumab: investigators' choice of chemotherapy), was designed to have adequate power for the co-primary analyses of overall response rate and overall survival, with an overall alpha of 0.05 two-sided and alpha allocation of 0.001, two-sided for the comparative analysis of overall response rate and 0.049 two-sided for the comparative analysis of overall survival.

A single, non-comparative interim analysis of overall response rate was to occur after 120 patients who received nivolumab had a minimum duration of follow up of 6 months. Determination of overall response rate will be based on confirmed objective response rate (ORR) as identified by blinded independent central review (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST 1.1). This analysis will be supported by IRC-determined duration of response. The interim analysis was to be conducted in 120 patients based on the assumption that a minimum of 30 responses (≥ 25% ORR) would need to be observed to rule out an ORR of <15% based on the lower bound of the 95% confidence interval.

A single interim analysis of overall survival is planned 169 deaths (65% of the total planned events). The final analysis of overall survival will occur after 260 deaths. The final analysis of overall survival (if not stopped at the interim analysis) will be performed after 260 deaths. The final analysis is powered to detect a hazard ratio of 0.65, with 90% power, assuming a median survival of 8 months in the control (chemotherapy) am and 12.3 months in the nivolumab arm. The stopping boundaries for the interim analysis was derived based on the Lan-DeMets alpha spending function with O'Brien-Fleming boundaries; the significance level for the interim OS analysis is 0.0105 and 0.0457 for the final OS analysis.

Results

The trial is fully accrued, with 631 enrolled across 90 clinical study sites in 14 countries, of these, 405 patients were eligible for randomization (272 patients allocated to nivolumab and 133 patients allocated to investigator's choice of chemotherapy). The first patient was enrolled in December 21, 2012. For the subgroup of 120 patients included in this interim analysis, the last study visit for assessment of response was March 10, 2014 and the clinical database lock was April 30, 2014.

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 progressed 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 has M1c disease , 22% had BRAF V600 mutation-positive melanoma, 56% had elevated LDH at baseline, 18% has a history of brain metastases, and all patients had 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), which consisted of four 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)], however as with the BRAF subgroups, these difference may be due to small numbers rather than true treatment differences and 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.

The clinical benefits observed [ORR 32% (95% CI: 23, 41) with one-third of responses lasting more than 6 months] is reasonably likely to predict clinical benefit in this patient population with an unmet medical need. Approval under the provisions of 21 CFR 601 Subpart E requires verification of clinical benefit which may be demonstrated either through a mature analysis of Protocol CA209037 or potentially other ongoing trials. BMS proposes to verify clinical benefit under the following PMR

> Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab 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.

8. Safety

Size of the database
The safety population consists of all patients who were randomized and received at least one dose of study-specified treatment: 268 patients randomized to nivolumab and 102 patients randomized to chemotherapy for clinical adverse events and all patients who were randomized and received at least one dose of study drug with baseline laboratory assessment and at least one follow-up measure for assessment of laboratory abnormalities. The safety database of 268 nivolumab-treated patients in randomized, open-label of Study CA209037 is adequate to detect adverse reactions occurring at an incidence of 1.5% or higher with up to six months of exposure. This is supplemented by data on serious adverse drug reactions in 306 patients with various solid tumors who received nivolumab at doses ranging from 0.1 to 10 mg/kg in Study CA209003. The greatest limitation of this database was the short duration of exposure in the controlled clinical trial, CA209037, with only 64 patients receiving nivolumab for more than 6 months and only 8 patients receiving nivolumab for more than one year.

Major safety concerns related to labeling
The most serious, including fatal, adverse reactions of nivolumab are investigator-determined, autoimmune-mediated organ toxicity, most commonly involving the lungs (3.4% overall; (b) (4)% 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.

Autoimmune-mediated organ toxicity is a diagnosis of exclusion, based on ruling out alternative etiologies (e.g., infection) and response to corticosteroids. The time to onset ranges from 1 to 6 months after initiation of nivolumab; some cases occurred after discontinuation of nivolumab for other reasons (e.g., disease progression). Prompt initiation of high-dose (1-2 mg/kg/day prednisone equivalents) corticosteroids and interruption or permanent discontinuation nivolumab appear to mitigate the autoimmune reaction. Insufficient experience was provided in the application to assess the likelihood of recurrence of

autoimmune-mediated organ toxicity with re-challenge, however based on the limited experience, some patients were able to tolerate resumption of nivolumab after complete resolution of symptoms and completion of corticosteroid taper.

Comparative data with complete datasets were provided only for Study CA209307 for evaluation of the incidence of adverse reactions of nivolumab. In this trial, safety data were provided for 268 patients received nivolumab 3 mg/kg every 2 weeks (n=268) and 102 patients received either dacarbazine 1000 mg/m^2 every 3 weeks or the combination of carboplatin AUC 6 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 was 2 months in chemotherapy-treated patients. As noted above, the adverse reaction profile with long-term exposure was not adequately characterized with data limited to only 64 (24%) patients who received nivolumab for more than 6 months and 8 (3%) patients who received nivolumab for more than 1 year.

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%)

The incidence of anti-nivolumab antibodies was 8.5% (24 of 281 patients receiving nivolumab 3 mg/kg every 2 weeks) and the incidence of neutralizing antibodies was 0.7% (2/24 patients). The development of anti-nivolumab antibodies did not appear to alter the pharmacokinetics or toxicity profile of nivolumab.

Final labeling recommendations
Development of labeling recommendations with regard to the incidence and description of autoimmune-mediated organ toxicity was challenging based on failure to develop case definitions and systematic approach to data collection for such events. The identification of cases for as autoimmune-mediated relied on the investigator-assessment, the basis for which were not captured in case report forms, the investigators' decision to initiate high-dose corticosteroids, and the absence of an alternative explanation (e.g., infection or disease progression) for organ dysfunction. This approach was used as the basis for capturing such cases in the product labeling, supplement by a comparative description of laboratory abnormalities (e.g., liver tests, creatinine) to place the cases in the context of background organ dysfunction that may not reflect breaking of tolerance to self-antigens.

REMS
The clinical reviewers and the DRISK consultant recommended, and I concur, that a Risk Evaluation and Mitigation Strategy was not required to ensure safe and effective use of nivolumab, considering the serious risks of autoimmune-mediated organ toxicity. This is the third drug whose mechanism of action is breaking tolerance to tumor and self-antigens, thus medical oncologists are more familiar with the recognition and management of this serious adverse reaction of nivolumab. While fatal pneumonitis occurred in (b) (4)% of patients in the

clinical development program, these cases were early in development and the incidence of fatal events appears to be decreasing with recommended medical management (high-dose corticosteroids).

PMRs and PMCs
No post-marketing requirements or commitments were requested for the further evaluation of the safety profile of nivolumab as such data will be provided in the study(ies) required to verify clinical benefit, which will be controlled clinical trials with a larger number of nivolumab-treated patients where exposure is expected to more closely reflect clinical use.

9. Advisory Committee Meeting

This BLA for a new molecular entity was not referred to the Oncologic Drugs Advisory Committee 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 to make a risk: benefit assessment or determine the acceptability of the risks in light of the benefits.

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 the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

Proprietary name: The proposed proprietary name, Opdivo, was found to be acceptable by the Office of Prescription Drug Promotion (ODPD), the Division of Oncology Products 2 (DOP2), and the Division of Medication Error and Prevention Analysis (DMEPA), based on the lack of potential for drug medication errors (look-alike/sound-alike errors) and lack of concern regarding promotional claims.

Physician labeling: All comments provided by the OPDP consultant were considered, and were appropriate, incorporated into product labeling. The modifications to BMS' proposed labeling are discussed below.

- Indications and Usage: The section was modified to include language stating that this was an accelerated approval and that clinical benefit has not been established. The indication was further revised to state that the product is indicated only for those patients with BRAF V600 mutation-positive melanoma who have received and have had disease progression on or following a BRAF inhibitor.

- Dosage and Administration: This section was edited to remove the stated that nivolumab administration should continue [redacted] and replaced with "until disease progression," since there were no patients in Study CA209037 who had clear evidence of response following initial disease progression. The Dose Modifications subsection was extensively revised for consistency with patient management for investigator-determined immune-mediated adverse reactions, which differed from the protocol-specified guidelines. In particular, dose modifications were not employed for most patients with immune-mediated hypo- or hyperthyroidism, description of dose modification based on positive re-challenge, and requirement for inability to taper corticosteroids within 12 weeks. The management of immune-mediated adverse reactions other than dose modification of nivolumab is described in section 5 of the product labeling. Edited the Preparation and Administration subsection for brevity and essential information. Deleted statement that [redacted]
- Dosage Forms and Strengths: Added dosage form (Injection) and that the product presentation is a single-use vial.
- Contraindications: No modifications
- Warnings and Precautions: Removed the [redacted] prior to specific Warnings and Precautions subsections to limit redundancy and avoid confusion. Re-ordered proposed Warnings in order of importance to patients and healthcare providers, starting with immune-mediated pneumonitis where the incidence of fatal pneumonitis was [redacted]% (based on incidence in 574 nivolumab-treated patients enrolled in one of two clinical trials with complete datasets for calculation of the incidence). Information on comparative incidence of clinical signs, symptoms, or laboratory abnormalities from CA209037 were provided, followed by the descriptive information on the number of patients identified by investigators as having immune-mediated adverse events in the nivolumab arm. For the latter subgroup, information on the time to onset, requirement for corticosteroids (high or low dose), duration of corticosteroid treatment prior to taper, need for other medical management, dose modifications for nivolumab, outcomes data (resolution or ongoing), and outcome of rechallenge were summarized where this could be gleaned from case report forms and narrative summaries. Under the subsection titled Other Immune-Mediated Adverse Reactions, a listing of other events reported across all clinical trials, including ongoing and double-blind clinical trials, were identified without incidence information. Adverse Reactions: This section was modified to (1) describe the integrated safety database with sufficient information to assess the incidence of risks, (2)demographic and exposure information on the safety population from Study CA209037, (3) revision of the tables to included only those adverse events or laboratory abnormalities which are possible adverse drug reactions based on higher incidence in the nivolumab-treated group as compared to the chemotherapy-group (e.g., fatigue), (4) deleted information in Section 6 on clinical course and management of autoimmune-mediated toxicities and incorporation of these data into Section 5 of the USPI, and (6) revisions to subsection on immunogenicity to include only the 281 patients rather than [redacted]

- Drug Interactions: Edited for essential information; deleted [redacted]
- Use in Specific Populations: Revised in accordance with Final Rule on Product Labeling for Pregnancy and Lactation; removed [redacted] as per the final rule; included description of potential risk to fetus based on animal data and expected placental transmission of IgG4 immunoglobulins; included subsection on females and males of reproductive potential; revised Geriatric Use subsection as per 21 CFR 201.57 based on efficacy assessment in less than 100 elderly patients; provided succinct basis for dose recommendations in patients with renal or hepatic impairment.
- Overdosage: No modifications.
- Description: Edited to include pharmacologic class and for brevity and clarity
- Clinical Pharmacology: (1) mechanism of action subsection edited for brevity, essential information, and data directly demonstrated with nivolumab. Removes unsupported and promotional statements [redacted] (2) pharmacokinetics subsection edited to include more details on population PK analysis and more detailed description of PK.
- Nonclinical Pharmacology/Toxicology: Subsection 13.1 revised to include information on fertility observed in toxicology studies; Subsection 13.2 revised to remove [redacted]
- Clinical Studies: Demographic information in table converted to text and [redacted] removed [redacted] description of Study CA209037 revised to include information on key eligibility criteria to provide context to the prescriber, removed [redacted] as ORR data are provided in the table, removed [redacted] removed [redacted] but included an affirmative statement that responses were observed in patients with and without BRAF mutation-positive melanoma; removed [redacted] as there is no clinical basis for inclusion of this recommendation; removed [redacted] n Study CA209003, [redacted]
- How Supplied: minor editorial changes
- Patient Counseling: Expanded to include information in Sections 5 and 8 of the USPI.

- Carton and immediate container labels: the carton and immediate container labeling was revised as requested by DMEP and DOP2 to conform to applicable regulations.

- Patient labeling/Medication guide: Bristol Myers Squibb proposed patient labeling for this product and agreed to modifications proposed by the clinical review staff, the Office of Prescription Drug Promotion, and the Patient Labeling Team for conformance with applicable regulations and guidances and the agreed-upon Physician Package Insert.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I recommend accelerated approval under the provisions of 21 CFR 601 Subpart E.

- Risk Benefit Assessment
  All members of the review team recommended approval of this application.

  Based on the results of Study 209037, nivolumab demonstrated an overall response rate of 32% which is durable for more than 6 months in approximately one-third of responding 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%).

  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. For patients with metastatic disease, which accounts for 4% all cases of melanoma, the 5-year survival drops to 16%. While there are several drugs that 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 responses, is reasonably likely to predicted prolongation in progression-free survival of a clinically important magnitude and potentially an improvement in overall survival. Furthermore, the observed response rate and durability of responses would not be expected with chemotherapeutic agents or aldesleukin. 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, albeit only with high dose corticosteroids.

  For the reasons discussed above, I have concluded that the observed response rate and response duration are reasonably likely to predict clinical benefit and that the benefits of nivolumab in this patient population outweigh its risks. Finally, I have concluded that a REMS is not required to ensure safe and effective use of nivolumab for the indicated population.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical review team and DRISK consultant that a Risk Evaluation and Mitigation Strategy (REMS) is not required to ensure safe and effective use of nivolumab in the indicated patient population, which can be adequately addressed through the US Package Insert (USPI) instructions for dose modification in the Dosage and Administration section of the labeling, description of the risks of autoimmune-mediated organ toxicity in the Warnings and Precautions section of the USPI, and the experience in the medical community managing this type of adverse reaction with two approved products (ipilimumab and pembrolizumab).

- Recommendation for other Post-marketing Requirements and Commitments
  - The quality review team recommended five post-marketing requirements to better characterize the drug product and evaluate for lot-to-lot consistency. These post-marketing commitments are described in Section 3 of this review

  - A post-marketing requirement under 21 CFR 601 Subpart E has been identified to verify the clinical benefit as follows:

    "Conduct and submit the results of a multicenter, randomized trial or trials establishing the superiority of nivolumab 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 is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA KEEGAN
12/19/2014