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*APPLICATION NUMBER:*

**125554Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	December 22, 2014
<b>From</b>	Marc Theoret, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # Supplement#</b>	BLA 125554
<b>Applicant</b>	Bristol-Meyers Squibb
<b>Date of Submission</b>	July 30, 2014
<b>PDUFA Goal Date</b>	March 30, 2015
<b>Proprietary Name / Established (USAN) names</b>	Opdivo / nivolumab
<b>Dosage forms / Strength</b>	3 mg/kg IV every 2 weeks
<b>Proposed Indication(s)</b>	treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status
<b>Recommended:</b>	Approval (21 CFR part 601, subpart E)

<b>Material Reviewed / Consultants</b>	<b>Primary/ Secondary Reviewer</b>
Clinical Review	Maitreyee Hazarika, M.D. and Meredith Chuk, M.D. / Marc Theoret, M.D.
Statistical Review	Sirisha L. Mushti, Ph.D. / Kun He, Ph.D.
Regulatory Project Manager	Meredith Libeg / Monica Hughes
Pharmacology Toxicology Review	Shawna L. Weiss, Ph.D./ Whitney Helms, Ph.D.
Product Reviews	Product: Joel Welch, Ph.D. / Laurie Graham, M.S. Quality Micro: (DS) Bo Chi Ph.D., (DP) Steven Fong, Ph.D. / Patricia Hughes, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Xianhua W. Cao, Ph.D. / Hong Zhao, Ph.D. Pharmacometrics: Hongshan Li, Ph.D. / Liang Zhao, Ph.D.
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## 1. Introduction

On July 30, 2014, Bristol-Myers Squibb (heretofore referred to as the Applicant) submitted Biologics License Application (BLA) 125554 for the proposed the indication treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. On September 11, 2014, FDA granted the Applicant's July 18, 2014 request for designation of nivolumab as Breakthrough Therapy, for the treatment of advanced (unresectable or metastatic) melanoma in patients whose disease has progressed on or after anti-CTLA-4 therapy and, if BRAF V600 mutation positive, on or after both a BRAF inhibitor (BRAFi) and anti-CTLA-4 therapy.

The Applicant relies on the results from Trial CA209037 to serve as the primary evidence in BLA 125554 to demonstrate the safety and efficacy of nivolumab. Trial CA209307 is an ongoing, multicenter, open-label, randomized (2:1), active-controlled trial of nivolumab vs. chemotherapy in patients with unresectable or metastatic melanoma refractory to ipilimumab and, if BRAF V600 mutation positive, to a BRAF inhibitor. Patients received nivolumab 3 mg/kg administered as an intravenous infusion every 2 weeks (n=268) or investigator's choice chemotherapy administered as an intravenous infusion(s) once every 3 weeks (n=102), either dacarbazine 1000 mg/m<sup>2</sup> or the combination of carboplatin AUC 6 plus paclitaxel 175 mg/m<sup>2</sup>.

The primary evidence of efficacy was a non-comparative single-arm analysis of the objective response rate and durations of response in the first 120 patients treated with nivolumab with a 6-month minimum duration of follow-up. Of these 120 nivolumab-treated patients, the blinded independent central review (BICR)-assessed, confirmed overall response rate (ORR) per RECIST version 1.1 was 31.7% (95% confidence interval (CI): 23.5, 40.8), consisting of 34 partial responses and 4 complete responses. Objective responses were ongoing in 87% (33/38) of the responders with durations of response (DOR) ranging from 2.6+ to 10+ months, including 13 patients with ongoing responses for greater than 6 months as of the data cutoff date. These results are similar in patients with and without BRAF V600 mutations.

A major consideration for this BLA is the durability of the objective responses, given the modest ORR observed in the indicated population at the recommended dose of 3 mg/kg once every two weeks. Analyses of ORR and DOR from Trial CA209003, which had a longer duration of follow-up, provides supportive evidence of the magnitude of the point estimate of ORR observed in Trial CA209037 and of the durability of responses with a median DOR of 22.9 months (95% CI: 12.9, not reached). In Trial CA209003, response durations ranged from 4.2 to 26.6+ months in the nivolumab dose-level cohorts of 0.1 mg/kg to 3 mg/kg Q2W arm. This is discussed in further detail in Section 7 of this review.

## 2. Background

- Indicated Population

Melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. In 2014, it is estimated that there will be 76,100 new melanoma cases and 9,710 deaths from melanoma in the U.S.<sup>1</sup> Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases.<sup>2</sup> Melanoma, once metastatic, carries a grim prognosis—the five year survival rate is historically less than 10%—and develops at a relatively early age which results in a substantial number of years of life lost per person.<sup>3</sup>

In general, FDA-approved treatment options in use for treatment of metastatic melanoma include immunotherapy (interleukin-2, ipilimumab, pembrolizumab), chemotherapy (DTIC), and, if BRAF V600 mutation positive, BRAF inhibitors (vemurafenib, dabrafenib) and/or a MEK inhibitor (trametinib). Only ipilimumab and vemurafenib have been demonstrated in clinical trials to prolong overall survival compared with conventional therapy (refer to Table Appendix A, modified from the FDA Clinical Review of BLA 125554, for description of treatment effects of FDA-approved therapies for metastatic melanoma). DTIC and interleukin-2 are FDA-approved products that could be considered available therapy for treatment of the indicated population; however, dacarbazine and interleukin-2 have not been formally studied in this treatment-refractory setting. Nevertheless, objective response rates with either product are low (< 20%) and neither has demonstrated an improvement in overall survival. Furthermore, treatment with interleukin-2 is associated with substantial on-treatment toxicity and is an appropriate therapeutic option only in a selected subgroup of patients.

With the FDA-approval of pembrolizumab on September 4, 2014, there is one approved drug for treatment of patients refractory to ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. However, FDA granted accelerated approval to pembrolizumab which does not preclude FDA approval of other drugs for this indication under the accelerated approval regulations. Specifically, pembrolizumab is not considered available therapy based on its approval on a surrogate endpoint under 21CFR601 subpart E (in the absence of post-approval

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<sup>1</sup> Siegel, R, J Ma, Z Zou, and A Jemal, 2014, Cancer Statistics, 2014, CA Cancer J Clin, 64:9-29.

<sup>2</sup> Howlader, N, AM Noone, M Krapcho, N Neyman, R Aminou, et al., 2012, SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/), based on November 2011 SEER data submission, posted to the SEER web site, 2012.

<sup>3</sup> Ekwueme, DU, GP Guy, C Li, SH Rim, P Parelkar et al., 2011, The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006, J Am Acad Dermatol, 65 (5 Suppl 1):S133-43.

studies verifying clinical benefit), and the proposed indication remains an unmet medical need.<sup>4</sup>

- Mechanism of Action/Pharmacology

Nivolumab is a monoclonal antibody that blocks PD-1. PD-1 is a member of the CD28 family of coreceptors and is expressed in an inducible manner, found mainly on T cells (CD4<sup>+</sup> and CD8<sup>+</sup>), NK cells, B cells, and activated monocytes.<sup>5</sup> Two ligands have been identified for PD-1, PD-L1 and PD-L2; expression of PD-L1 is present on hematopoietic cells, including T cells, B cells, dendritic cells, macrophages, as well as nonhematopoietic cells while the expression of PD-L2 appears to be relatively limited to antigen-presenting cells. As a negative regulator of T-cell responses, PD-1 is upregulated on T cells following antigen-specific stimulation and, upon subsequent binding to PD-1 ligands, recruits SH2-domain containing tyrosine phosphatase (SHP2) thereby inhibiting T-cell receptor signaling and attenuating downstream T-cell proliferation and cytokine production.<sup>6</sup> In addition, other mechanisms for dampening the immune response have been described for the PD-1 pathway.<sup>7</sup> Blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2, can release the PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response.

- Key Regulatory History

Date	IND	Milestone
April 28, 2006	100052	Type B, Pre-IND Meeting to discuss MDX-1106 for the proposed indication non-small cell lung cancer, colorectal cancer, malignant melanoma, renal cancer, and (b) (4)
June 29, 2006	100052	FDA receipt of Original IND
February 7, 2012	100052	Type B, End-of-Phase 2 CMC meeting
June 19, 2012	115195	Original IND submission for investigation of BMS-936558/MDX-1106 for the melanoma indication.
July 17, 2012	115195	Type B, End-of-Phase 2 Meeting to discuss preliminary data from CA209003, to obtain guidance on development plan for second-line metastatic melanoma (CA209037), and to discuss potential for accelerated approval pathway for metastatic melanoma*

<sup>4</sup> FDA guidance for industry, 2014, Expedited Programs for Serious Conditions –Drugs and Biologics

<sup>5</sup> Reviewed in Kamphorst, AO, and RAhmed, 2013, Manipulating the PD-1 pathway to improve immunity, *Curr Opin Immunol*, 25:381-388.

<sup>6</sup> Reviewed in Okazaki, T, S Chikuma, Y Iwai, S Fagarasan, and T Honjo, 2013, A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application, *Nat Immunol*, 14:1212-1218.

<sup>7</sup> Reviewed in Sharpe, AH, EJ Wherry, RAhmed, and GJ Freeman, 2007, The function of programmed cell death 1 and its ligands in regulating autoimmunity and infection.

Date	IND	Milestone
October 4, 2012	115195	FDA designated as a Fast Track development program the investigation of BMS-936558/MDX-1106 for treatment of patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.
December 13, 2012	100052	Type C, Guidance meeting scheduled to discuss drug substance manufacturing process change and a new drug product presentation (meeting cancelled by BMS on December 12 because of agreement with FDA's preliminary responses).
January 23, 2013	115195	Deny request for breakthrough therapy designation*
January 23, 2013	-	Grant orphan drug designation*
July 18, 2013	-	Informal teleconference with the Applicant to determine its plan for submission of an expanded access program and to update FDA on its plan for a BLA submission.
October 3, 2013	104225	Type C Meeting to discuss global registration strategy and potential initiation of expanded access program for single-agent nivolumab in non-small cell lung cancer, melanoma, and renal cell carcinoma.
April 18, 2014	100052	Type B, Pre-BLA CMC meeting to discuss CMC plans for registration package to support potential accelerated approval of nivolumab.
May 8, 2014	115195	Applicant informed that the expanded access protocol of nivolumab for patients with unresectable or metastatic melanoma progressing post prior systemic treatment containing an anti-CTLA-4 monoclonal antibody may proceed.
July 9, 2014	115195	Type B, Pre-BLA meeting
September 11, 2014	115195	Grant request for breakthrough designation of nivolumab (refer to Section 1)

\*(see FDA Clinical Review, Section 2.5 for details).

Refer to Section 7 of this review and to the FDA Clinical Review for details of the regulatory history specific to the design and conduct of Trial CA209037.

### 3. CMC/Device

The primary reviewer of the product quality sections of the BLA was Joel Welch, Ph.D., from the Division of Monoclonal Antibodies (DMA). The product quality reviewer recommended approval of Opdivo (nivolumab) for human use (under conditions specified in the package insert). This recommendation was based on the conclusion that the data submitted in the BLA supports that

the manufacture of Opdivo (nivolumab) is well controlled and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents

sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured from multiple production runs.

The primary product quality review recommended an expiry period of (b) (4) months for nivolumab drug substances (DS) manufactured in the Lonza Biologics Incorporated facility (Portsmouth, New Hampshire) when stored at (b) (4). DMA recommended an expiry period of 24 months for nivolumab drug product (DP) when stored at 2-8°C.

Of note, FDA held a teleconference with the Applicant on September 15, 2014, to discuss the manufacturing and testing facilities sites included in the original BLA submitted on July 30, 2014. FDA noted that it did not have an inspectional history with the Lonza, Porrino, Spain facility site and requested clarification of the activities performed. BMS indicated that the Porrino, Spain site is an alternative testing site to the Portsmouth, New Hampshire, US site. On September 26, 2014, BMS amended the drug substance manufacturer section of BLA 125554 to remove Lonza Biologics, Porrino, Spain as a test site.

- General product quality considerations

Dr. Chi and Dr. Hughes recommended approval of nivolumab DS from a quality microbiology perspective. Dr. Fong and Dr. Hughes recommend approval from a product quality microbiology perspective (drug product).

Nivolumab is a human IgG4κ monoclonal antibody consisting of (b) (4). The molecular weight of nivolumab is calculated to be 146 kilodaltons (kDa).

Nivolumab DS is manufactured in the Lonza Biologics, Inc. facility (Portsmouth, NH; FEI 3001451441). Nivolumab is produced in (b) (4) and is formulated as an aqueous solution containing nivolumab (b) (4) in Sodium Citrate, (b) (4) Sodium Chloride, (b) (4) Mannitol, (b) (4) Pentetic Acid, (b) (4) Polysorbate 80, pH 6.0.

Nivolumab DP is manufactured at the Bristol-Myers Squibb Holdings Pharma, Ltd (Manati, Puerto Rico; FEI 2650089) facility. The composition of nivolumab DP is a sterile, single-use, preservative-free, isotonic aqueous solution. The solution is clear to opalescent with a colorless to pale yellow tint, packaged in (b) (4).

The composition of the 40 mg/ml and the 100 mg/10 mL presentations of nivolumab DP are as follows:

40 mg/4 mL format

Nivolumab (b) (4) sodium citrate dehydrate (b) (4) sodium chloride (b) (4) mannitol (b) (4) pentetic acid (b) (4) polysorbate 80 (b) (4) hydrochloric acid (b) (4) to pH 6.0 (pH adjustment), sodium hydroxide (b) (4) to pH 6.0 (pH adjustment), WFI (b) (4), to (b) (4) and (b) (4)

100 mg/10 mL format

Nivolumab (b) (4) sodium citrate dehydrate (b) (4) sodium chloride (b) (4) mannitol (b) (4) pentetic acid (b) (4), polysorbate 80 (b) (4) hydrochloric acid (b) (4) to pH 6.0, sodium hydroxide (b) (4) to pH 6.0, WFI (b) (4), to (b) (4) and (b) (4)

- Facilities review/inspection

FDA conducted pre-license inspections of nivolumab DS at Lonza (Portsmouth, NH) on September 29, 2014, through October 3, 2014, by the Biotechnology Manufacturing Assessment Branch (BMAB; Donald Obenhuber, Ph.D.) and Division of Monoclonal Antibodies (DMA; Joel Welch, Ph.D.). FDA issued a four-item Form FDA 483 at the end of the inspection, specifically: (1) validation of a bioburden assay using a diluent that does not undergo routine testing to ensure that it has no antimicrobial effects, (2) inadequate stability program timeframes, (3) discrepancies between the BLA 125554 submission and operations at the Lonza Portsmouth facility, and (4) inadequate cleaning validation program. See TB-EER for GMP status of the facility.

Drs. Steven Fong and Joel Welch from BMAB and DMA, respectively, recommended waiver of the pre-approval inspection of the drug product manufacturing site, Bristol-Myers Squibb Holdings Pharma, Ltd. (BMS-Manati), based on the compliance history of the firm, the current GMP status, the fact that this facility has been approved to manufacture multiple CDER products using the same manufacturing process. Thus, FDA waived the pre-license inspection of this site.

#### **4. Nonclinical Pharmacology/Toxicology**

Shawna Weis, Ph.D. and Alex Putnam, Ph.D., the primary nonclinical reviewers, Whitney Helms, Ph.D., the secondary reviewer, and John Leighton, Ph.D., the tertiary reviewer, concluded that the pharmacology and toxicology data in the BLA support the approval of nivolumab for the proposed indication from the nonclinical perspective.

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

Nivolumab binds human and cynomolgus monkey PD-1 with affinity of 3.06 nM and 3.92 nM, respectively, based on surface plasmon resonance; the ability of nivolumab to bind human

PD-1 was also evaluated using an enzyme-linked immunosorbent assay, which demonstrated saturable binding to human PD-1-Ig with an EC<sub>50</sub> of 0.39 nM.

The Applicant evaluated the ability of nivolumab to block binding of PD-L1 and PD-L2 to human PD-1, to antibody-dependent cell-mediated cytotoxicity (ADCC), and to promote complement dependent cytotoxicity (CDC). FACS analysis of transfected CHO cells expressing human PD-1 demonstrated that nivolumab blocked PD-L1 (EC<sub>50</sub> 1 nM) and PD-L2 (EC<sub>50</sub> 1 nM) binding to human PD-1. Nivolumab did not demonstrate ADCC against activated CD4<sup>+</sup> T cells using the DELFIA cell cytotoxicity kit. In a cell viability assay, nivolumab did not exhibit CDC against activated human CD4<sup>+</sup> T cells.

The Applicant identified three amino acid sequences recognized by nivolumab based on protease digestion of PD-1 and immunoprecipitation by nivolumab. The three peptides identified were, as follows: 1a (62-69), 1b (70-86), and 2 (118-136). The strongest affinity to nivolumab was peptide 1a. The nonclinical reviewer commented that the binding of nivolumab to antigen is likely dependent on glycosylation of PD-1 since nivolumab does not bind to nonglycosylated human PD-1 expressed in *E. coli* but bound only to glycosylated human PD-1 expressed in a mammalian cell line.

In pharmacodynamic studies, the Applicant performed *in vitro* studies with nivolumab with whole blood from humans. Nivolumab enhanced cytokine production in an allogeneic mixed lymphocyte reaction as measured by IFN- $\gamma$  secretion and T-cell proliferation (relative to a control antibody). In *ex vivo* cytokine expression studies with human peripheral blood cells, analysis of fresh human blood samples (healthy subjects) incubated with nivolumab or control antibody demonstrated no significant effect on release of IFN- $\gamma$ , TNF- $\alpha$ , IL-2, IL-6, and IL-10. The applicant used a surrogate molecule [chimeric (rat VL and VH sequences grafted onto murine kappa and IgG1 Fc region) anti-mouse-PD-1 antibody (identified as 4H2)] for *in vivo* tumor studies. In these studies, administration of 4H2 compared to control(s) to mice bearing J558 mouse myeloma, MC38, SA1/N murine fibrosarcoma, Renca (renal cell carcinoma, 4T1 (breast carcinoma), CT26 (colon carcinoma), and B16.F10 (melanoma) demonstrated variable effects on tumor (refer to FDA Pharmacology/Toxicology Review).

In selection of the relevant toxicological species, the Applicant confirmed binding of nivolumab to human PD-1 with fluorescence-activated cell sorting (FACS) analysis of transfected CHO cells (EC<sub>50</sub> 1.7 nM) and activated human CD4<sup>+</sup> T cells (EC<sub>50</sub> 0.64 nM) expressing cell surface PD-1. Binding of nivolumab to cynomolgus monkey PD-1 was confirmed by FACS analysis of activated monkey splenocytes. Flow cytometry studies demonstrated absence of nivolumab binding to activated rat and rabbit splenocytes.

The FDA Nonclinical Reviewer described the findings from two repeat-dose toxicology studies, a 4-week (nivolumab doses of 0, 1, 10, 50 mg/kg administered weekly for four doses) and a 13-week study (nivolumab doses of 0, 10, and 50 mg/kg administered twice weekly), conducted in cynomolgus monkeys. As stated in the review, these studies demonstrated a diffuse pattern of inflammatory infiltration in organs and tissues, but clinical pathology and histological analysis did not identify target organ toxicity; however, there was a trend towards increased in CD4<sup>+</sup> and CD8<sup>+</sup> memory T cells in the high-dose group (50 mg/kg), consistent

with its mechanism of action. Findings were similar in the cynomolgus monkeys receiving weekly and twice-weekly intravenous injection schedules of administration for up to 13 weeks. Both studies demonstrated no pre-term deaths. In the 13-week study, T3 and TSH levels were decreased in high-dose females; this laboratory finding was not associated with alterations in T4 levels or histological evidence of thyroid pathology.

- Carcinogenicity

The Applicant did not conduct carcinogenicity studies with nivolumab, which is consistent with its use in patients with advanced cancer (refer to International Conference on Harmonization Guideline S9 Nonclinical Evaluation of Anticancer Pharmaceuticals).

- Reproductive toxicology

The Applicant performed a pre- and post-natal development study in cynomolgus monkeys with a 6-month postnatal evaluation. Key findings from this study were excerpted from the FDA Pharmacology/Toxicology BLA Review:

- Administration of BMS936558 was associated with a dose-related increase in pregnancy loss, particularly during the third trimester. The rate of pregnancy loss in this study exceeded the average historical control frequency, and the individual study incidence noted in historical controls, and is considered treatment-related
  - Aside from one umbilical thrombus noted in one 50 mg/kg female that aborted on GD47, no cause was ascribed to any of the first-trimester pregnancy losses, and all evaluable fetuses/stillbirths appeared normal.
  - Three of the 4 infants lost in the 10 mg/kg dose group were delivered prematurely (GD 131, 135 and 143) and died within the first two weeks.
  - There were no clear treatment-related gross or histopathological lesions in infants that died prior to scheduled termination; the cause of death was ascribed to prematurity and failure to thrive.
  - Toxicokinetic exposure was maintained in most dams and high-dose infants through the end of the study (PPD 182±1)
- Other notable issues (resolved or outstanding)

The FDA nonclinical reviewers described two other notable potential issues: (1) detrimental alterations in the immune response to pathogens and (2) increased antigen responsiveness to vaccination.

The following was excerpted from the FDA Pharmacology/Toxicology BLA Secondary Review [note: references provided in review]:

In addition to the antigen response study included in the pre- and postnatal development study, the Applicant conducted additional ex vivo and in vivo investigations into the mechanism of action of nivolumab and potential effects on immune function following primary and secondary antigen exposure in the presence of the antibody. Ex vivo studies using human PBMCs demonstrated increased antigen

responsiveness in the presence of nivolumab. Increases were noted not only following primary immune activation, demonstrated in mixed lymphocyte reaction studies, but also in response to previously recognized antigens including cytomegalovirus and chronic hepatitis virus. An increase in sensitivity to pulmonary rechallenge by ovalbumin was also demonstrated in a mouse PD-1 knockout model. Finally, there are published reports showing that the absence of PD-1 signaling can result in detrimental alterations in the immune response to pathogens. Notably, infection of PD-1 deficient mice with tuberculosis was associated with a decrease in survival compared to wild type animals<sup>1</sup>. Similarly, decreases in survival have been reported in mouse models of lymphocytic choriomeningitis virus (LCMV) infection, though the etiology of these decreases is different between the types of infection<sup>2-3</sup>. Collectively the data from the rechallenge and infection models is consistent with the potential for increased nivolumab-mediated toxicity following second exposure to an antigen in the presence of the antibody or following administration of nivolumab to virally-infected patients. Data describing these animal models of infection are recommended for inclusion in Section 13.2 of the label.

The FDA Pharmacology/Toxicology Reviewers do not recommend any postmarketing requirements or postmarketing commitments.

## 5. Clinical Pharmacology/Biopharmaceutics

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The FDA Clinical Pharmacology Review Team recommended approval of the BLA from the clinical pharmacology perspective. The Office of Clinical Pharmacology did not recommend any post-marketing requirements or commitments.

The following summary of the PK characteristics of nivolumab is excerpted from the FDA Clinical Pharmacology Review:

The PK profile of nivolumab has been characterized by non-compartment analysis (NCA) and population PK (PPK) analysis based on the data from clinical studies as described in Table 1. PPK analysis (with n=909 nivolumab treated patients) indicates that the PK of nivolumab is time-invariant and linear in the dose range of 0.1 to 20 mg/kg. The volume of distribution of nivolumab at steady state is 8 L with a variability of 30.4%. The systemic clearance (CL) is 9.5 mL/hr with a variability of 50%. The terminal half-life ( $t_{1/2}$ ) was estimated to be 26.7 days and steady-state was achieved by 12 weeks of Q2W repeated dosing. The accumulation index (AI) of 3 mg/kg Q2W dosing regimen is estimated to be approximately 3-fold.

- Drug-drug interactions

The FDA Clinical Pharmacology reviewer described the possibility of drug-drug interactions as unlikely, either as a direct mechanism considering the elimination pathway of a therapeutic

monoclonal antibody or as an indirect mechanism as nivolumab is not considered a modulator of cytokines which may affect drug metabolizing enzymes or transporters.

- Pathway of elimination

As a therapeutic monoclonal antibody, nivolumab is expected to be catabolized into amino acids by general protein degradation process.

- Demographic interactions/special populations

The FDA Clinical Pharmacology Review assessed the effects of various covariates on the PK of nivolumab in population pharmacokinetic analyses. In summary, the FDA Clinical Pharmacology review did not identify any clinically important effect on the clearance of nivolumab in analyses of the following intrinsic factors (description of analysis populations):

- Age (range 23 to 87 years, n=909)
- Gender (men, n=603; women, n=306)
- Race (White, n=793; Asian, n=67; Black, n=40; Other, n=9)
- Baseline LDH
- PD-L1 expression
- Tumor type
- Tumor size
- Immunogenicity
- Renal impairment (eGFR 60-90 mL/min/m<sup>2</sup> [mild], n=313; eGFR 30-59 mL/min/m<sup>2</sup> [moderate], n=140; eGFR < 30 L/min/m<sup>2</sup> [severe], n=3)
- Mild hepatic impairment (total bilirubin [TB] ≤ upper limit of normal [ULN] and AST > ULN or TB between 1.0 to 1.5 times ULN and any AST, n=92)

Of note, population PK analyses identified bodyweight (ranged from 34 to 162 kg with a mean weight of 81 kg) as a statistically significant covariate on nivolumab clearance and central volume of distribution; however, nivolumab exposures (i.e., dose normalized C<sub>avg,ss</sub> and C<sub>min,ss</sub>) were noted by the FDA Clinical Pharmacology Reviewer to be approximately uniform with bodyweight-based dosing (mg/kg based).

- Thorough QT study or other QT assessment

The Applicant performed a QT substudy as part of a three-arm, randomized, dose-ranging trial of nivolumab (0.3, 2, and 10 mg/kg every 3 weeks) in patients with solid tumors. There was no dose response for QTcF, ΔQTcF, or change from baseline in heart rate, PR interval, or QRS interval after either first dose or seventh dose of nivolumab. In addition, no patients had a QTcF interval > 470 msec or a ΔQTcF of > 45 msec.

- Other notable issues (resolved or outstanding)

### Dose Selection

The FDA Clinical Pharmacology review summarized the Applicant's dosage selection of 3 mg/kg administered once every 2 weeks based on an ex vivo receptor binding study, animal tumor models, and clinical dose-escalation trial of patients with various solid tumor types (CA209003). Nivolumab at a dose of 3 mg/kg dose was able to saturate the PD-1 receptor. In addition, efficacious doses of nivolumab in preclinical models suggest a human equivalent efficacy dose of 1 to 3 mg/kg administered on an every 2-week schedule. Lastly, nivolumab administered at a range of doses in Trial CA209003 demonstrated no trend in exposure-response relationship for anti-tumor activity or safety—3 mg/kg of nivolumab administered every 2 weeks was noted to be safe and efficacious.

### Exposure-Response Analyses

The FDA Clinical Pharmacology review described the exposure ( $C_{avg,ss}$ )-response relationship for ORR and for adverse as flat. In the dose-escalation Trial CA209003, there was a flat exposure-response relationship over the dose range of 0.1 mg/kg to 10 mg/kg for ORR. In addition, population PK modeling in Study CA209037 demonstrated a flat exposure-efficacy relationship between individual exposures and ORR. Similarly, analyses of Trial CA209307 demonstrated no exposure-safety relationships between exposure ( $C_{avg,ss}$ ) and time to first drug-related Grade  $\geq 3$ , all causality Grade  $\geq 3$  adverse events, and AEs leading to discontinuation.

### Immunogenicity

According to the FDA Clinical Pharmacology Reviewer, there was no apparent altered pharmacokinetic profile, toxicity profile, or efficacy associated with anti-product antibodies (APA). Of the 281 patients who received nivolumab 3 mg/kg every two weeks, 8.5% (24/281) of patients tested positive for treatment-emergent APA using a third generation electrochemiluminescence assay with sufficient drug tolerance (800 ug/mL, which exceeds the expected trough levels of nivolumab 3 mg/kg administered every 2 weeks). Of these 24 patients, two were persistently positive for APA and two patients tested positive for neutralizing antibodies to nivolumab. Nivolumab clearance in patients who tested positive for APA was in the range of clearance for patients who tested negative for APA. In the two patients who tested positive for neutralizing antibodies, nivolumab concentrations increased at subsequent assessments when neutralizing antibodies were not detectable. None of the patients with treatment-emergent APA experienced any hypersensitivity events (such as anaphylaxis, urticaria, angioedema, or injection site reactions) associated with APA.

## **6. Clinical Microbiology**

The section is not applicable to the review.

## 7. Clinical/Statistical- Efficacy

I agree with the overall conclusions of the primary FDA Clinical Reviewer for efficacy, Dr. Meredith Chuk, and of the primary FDA Statistical Reviewer, Dr. Sirisha Mushti, pertaining to the efficacy data submitted in the BLA to support an indication for nivolumab for treatment of patients with unresectable or metastatic melanoma who had disease progression following ipilimumab treatment and, if BRAF V600 mutation positive, a BRAF inhibitor. The following postmarketing requirement is recommended to fulfill the requirements under 21 CFR part 601, subpart E to verify and describe the clinical benefit of nivolumab:

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.

- **Efficacy Summary**

The Applicant submitted data and results of Trial CA209037 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”, an ongoing, multicenter, open-label, randomized, active-controlled trial of nivolumab compared with chemotherapy in patients with treatment-refractory, unresectable or metastatic melanoma who have disease progression following an ipilimumab therapy (completed at least 6 weeks prior to enrollment) and, if BRAF V600 mutation positive, a BRAF inhibitor (any sequence).

The trial randomized (2:1) patients to receive:

- Nivolumab 3 mg/kg administered as an intravenous infusion over 60 minutes on Day 1 of an every 2-week cycle (n=272) or
- Investigator’s choice chemotherapy (n=133), either dacarbazine 1000 mg/m<sup>2</sup> administered as an intravenous infusion over 30-60 minutes on Day 1 of an every 3-week cycle or carboplatin AUC 6 administered as an intravenous infusion over 30 minutes in combination with paclitaxel 175 mg/m<sup>2</sup> administered as an intravenous infusion over 180 minutes on Day 1 of an every 3-week cycle.

Treatment was administered until progressive disease or unacceptable toxicity.

Randomization stratification factors were PD-L1 status (positive based on  $\geq 5\%$  tumor cell membrane staining vs. negative based on  $<5\%$  tumor cell membrane staining in a minimum of 100 cells), BRAF status (wild-type vs. mutation positive), and best response to prior anti-CTLA-4 therapy (best overall response of complete response, partial response, or stable disease vs. best overall response of progressive disease).

The primary objectives of Trial CA209037 are (1) to estimate the objective response rate (ORR) in the nivolumab group (i.e., a non-comparative assessment of the first 120 nivolumab-treated subjects with a minimum of 6 months follow-up) and (2) to compare the overall survival (OS) of nivolumab to investigator’s choice. Secondary objectives are to (1) compare the progression-free survival (PFS) of BMS-936558 (nivolumab) to investigator’s choice in

subjects with advanced melanoma, (2) evaluate whether PD-L1 expression is a predictive biomarker for ORR and OS, and (3) evaluate Health Related Quality of Life (HRQoL) as assessed by EORTC QLQ-C30.

Key inclusion criteria were:

- Histologically confirmed Stage III (unresectable) or Stage IV melanoma
- ECOG Performance Status of 0 or 1
- Measurable disease per RECIST 1.1
- Pre-treatment tumor tissue specimen for PD-L1 status

Key exclusion criteria related to prior ipilimumab, were:

- Grade 4 anti-CTLA-4 therapy related adverse reaction (except nausea, fatigue, infusion reactions, or endocrinopathies controlled on hormone replacement therapy) and Grade 3 anti-CTLA-4 therapy related adverse reactions that have not resolved or been controlled within 12 weeks
- Grade  $\geq 2$  eye pain or reduction of visual acuity that did not respond to topical therapy and did not improve to Grade  $\leq 1$  severity within 2 weeks of starting topical therapy or required systemic treatment
- Grade  $\geq 3$  sensory neurologic toxicity
- AST or ALT  $> 10$  x upper limit of normal (ULN), total bilirubin  $> 5$  x ULN, or any Grade 4 laboratory abnormalities
- History of drug-related toxicities requiring management with infliximab or other immunosuppressive medications

Key general exclusion criteria were:

- Active brain or leptomeningeal metastases (previously treated, clinically stable brain metastases without progression for at least 8 weeks and not requiring immunosuppressive doses of corticosteroids permitted)
- Active, known, or suspected autoimmune disease
- Syndrome that requires systemic corticosteroids ( $> 10$  mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of drug administration
- HIV positivity, active hepatitis B or hepatitis C
- Prior treatment targeting the PD-1:PD-L1 pathway or prior systemic therapy with both dacarbazine and carboplatin plus paclitaxel.

The sample size calculations accounted for the co-primary endpoints: ORR and OS with an alpha allocation of 0.1% and 4.9%, respectively. Formal analysis of the co-primary endpoints will occur at different time points with the ORR endpoint being analyzed first followed by the interim and final OS analyses.

Tumor assessments were scheduled at Week 9 and then every 6 weeks for the first year and every 12 weeks thereafter. The ORR endpoint will be analyzed at the time the first 120 patients treated on the nivolumab arm will have a minimum follow-up of 6 months. ORR as assessed by a blinded independent central review (BICR) per RECIST v 1.1 is defined as the number of subjects whose confirmed best objective (BOR) response is a complete response (CR) or partial response (PR), divided by the number of subjects in the population of interest. As described in the FDA Statistical Review, a total of 120 subjects achieves a maximum width of 17.1% for the exact two-sided 95% confidence interval (CI) when the ORR is expected to

be in the 5% to 30% range; a sample size of 120 patients was chosen such that the lower-limit of the exact 95% confidence interval excludes a response rate of 15% or less.

**REVIEWER COMMENT:**

*The Applicant modified the design of the CA209037 trial from a comparative analysis of ORR to demonstrate superiority of nivolumab vs. chemotherapy to a non-comparative single-arm estimation of ORR in the nivolumab treated group. This modification in the primary analysis of the ORR co-primary endpoint followed several interactions with FDA as discussed in Section 2.5 of the FDA Clinical BLA Review and supplemented below:*

- *October 3, 2013 Type C meeting to discuss the development program of nivolumab—the Applicant proposed to “decouple” the comparative analysis of ORR (nivolumab arm vs. investigator’s choice chemotherapy arm) from the timing of the planned interim analysis of OS*
- *October 25, 2013 submission of a statistical analysis plan (SAP) incorporating a (1) revision of the alpha allocation for the co-primary endpoints (ORR and OS) and changes in the sample size calculation; (2) timing change for the interim analysis of OS which will be later than the final analysis of ORR, and (3) change of the analysis population for ORR*
- *January 6, 2014 submission of revised protocol incorporating the changes described in the October 25, 2013 SAP.*
- *In an Advice/Information Request Letter dated January 16, 2014, FDA informed the Applicant that it did not agree with the revised alpha allocation for the co-primary endpoints and recommended that the Applicant modify the alpha allocation to 0.01:0.04 for ORR:OS as originally planned. FDA also disagreed with the Applicant’s proposal to change the primary method of assessment of ORR from BICR to investigator. Lastly, FDA provided the Applicant with options to consider for accelerating the timeline for the ORR analysis.*
- *February 6, 2014 teleconference held under parent IND (100052) for nivolumab—the Applicant proposes modifications to the primary analysis of ORR—FDA requested that the Applicant provide details of this proposal. In a general correspondence submitted February 13, 2014, the Applicant provided confirmation that the alpha allocation will be restored to the original allocation plan and provided details of the non-comparative primary analysis of ORR, i.e., a non-comparative, single-arm estimation of ORR with a 99% confidence interval in the first 120 treated patients on the nivolumab arm.*
- *On March 17, 2014, FDA sent the Applicant an Advice/Information Request letter stating that a proposal to modify the analysis of confirmed ORR based on independent review in 120 nivolumab-treated patients, with a goal of excluding an overall response rate of less than 15% (based on the lower 99% confidence interval) was acceptable. On May 23, 2014, the Applicant submitted the revised protocol incorporating the non-comparative single-arm analysis of ORR in the first 120 nivolumab-treated patients with a minimum duration of follow-up of 6 months.*

The formal analysis of OS will be performed in the intent-to-treat (all randomized) population. OS is defined as the time from randomization to the date of death. Among the estimated 390 randomized subjects, at least 260 death events are required to provide 90% power to detect an OS hazard ratio of 0.65, corresponding to a median OS of 8 months vs. 12.3 months for the

investigator’s choice chemotherapy arm and nivolumab arm, respectively, with an overall two-side type I error of 4.9%.

Secondary endpoints are PFS defined as the time from randomization to the date of the first documented progression as assessed by BICR per RECIST 1.1, or death due to any cause, whichever occurs first; (2) PD-L1 expression defined as the percent of tumor cells membrane staining in a minimum of 100 evaluable tumor cells to evaluate this secondary objective; and (3) Health-related quality of life as assessed by the EORTC QLQ-C30 (version 3).

*Trial CA209037 Results*

Trial CA209037 randomized (2:1) 405 patients to receive nivolumab 3 mg/kg administered as an intravenous infusion over 60 minutes on Day 1 of an every 2-week cycle (n=272) or investigator’s choice chemotherapy (n=133). The primary efficacy analysis population for the ORR co-primary endpoint is the first 120 nivolumab-treated patients with a minimum duration of follow-up of 6 months. Of these 120 patients, the median age was 58 years (32% age 65 or older); 65% were male; 98% were White; and 58% and 42% had an ECOG performance status 0 and 1, respectively; 22% had a BRAF V600 mutation; 56% had an elevated lactate dehydrogenase at baseline; 76% were M1c category; 18% had a history of brain metastases; and 68% had two or more prior therapies for advanced or metastatic disease.

The BICR-assessed ORR by RECIST 1.1 was 31.7% (95% CI: 23.5, 40.8) in the 120 nivolumab-treated patients; 3.3% (4/120) of patients had a CR and 28.3% (34/120) of patients had a PR. The median duration of response (DOR) was not reached with durations of responses ranging from 1.4 months to 10+ months. Responses were ongoing in 87% (33/38) of patients with an objective response, which includes 13 patients with ongoing responses of greater than 6 months, as listed in Table 2.

**Table 1: Durations of Response by BICR per RECIST 1.1, Nivolumab-Treated Patients, Trial CA209037**

Patient ID	Duration of response in months
CA209037-2-37115a	1.4
CA209037-77-37142a	1.5
CA209037-44-37297b	3.8
CA209037-30-37309c	4.4
CA209037-50-37006a	5.6
CA209037-10-37222	2.6+
CA209037-15-37264	2.8+
CA209037-16-37063	2.8+
CA209037-34-37228	2.8+
CA209037-50-37235	2.8+
CA209037-51-37261	3.2+
CA209037-77-37249	4.0+
CA209037-23-37196	4.1+

CA209037-28-37020	4.2+
CA209037-36-37199	4.2+
CA209037-16-37181d	4.6+
CA209037-47-37184	5.4+
CA209037-39-37154	5.5+
CA209037-1-37156	5.5+
CA209037-20-37098	5.6+
CA209037-27-37046	5.6+
CA209037-87-37183	5.6+
CA209037-73-37163	5.7+
CA209037-28-37164	5.8+
CA209037-43-37159d	5.8+
CA209037-36-37083	6.9+
CA209037-10-37061	6.9+
CA209037-10-37086	6.9+
CA209037-28-37117	6.9+
CA209037-63-37087	7+
CA209037-27-37097	7.1+
CA209037-16-37005	7.2+
CA209037-9-37091	7.2+
CA209037-51-37064	8.1+
CA209037-35-37047d	8.3+
CA209037-30-37025	9.7+
CA209037-28-37021	9.8+
CA209037-50-37008	10+

Source: Reproduced from FDA Clinical Review (as adapted from FDA Statistical Review, CRFs)

+ indicates subjects with an ongoing response at the time of data cutoff

<sup>a</sup> Patient received subsequent therapy and was censored by BICR at time of therapy

<sup>b</sup> Patient had disease progression

<sup>c</sup> Patient died

<sup>d</sup> Patient progression-free in follow up [CA209037-16-37181: off-treatment for non-compliance; CA209037-43-37159: off-treatment for toxicity (arthritis); CA209037-35-37047: off-treatment at request of patient for toxicity]

In the analyses performed by the FDA statistical reviewer, the BICR-assessed ORR was similar across subgroups based on key demographics and baseline disease characteristics. Although the numbers are relatively small, 23% (6/26) of patients with BRAF V600 mutation-positive melanoma also experienced objective responses. In addition, 22% (14/65) of patients with negative/indeterminate PD-L1 expression (based on randomization strata) experienced objective responses. In a sensitivity analysis, the investigator-assessed ORR of 25.8% (95% CI: 18.3, 34.6) in the first 120 nivolumab-treated patients was supportive of the primary ORR analysis.

The Applicant provided a descriptive analysis of confirmed ORR as assessed by BICR per RECIST 1.1 in the investigator's choice chemotherapy-treated group with a minimum duration of follow-up of 6 months (n=47). This analysis demonstrated an ORR of 10.6% (95% CI: 3.5,

23.1) with a median duration of response of 3.6 months (range 1.3+, 3.5). Refer to the FDA Clinical Review for additional details of the subgroup.

Non-comparative, preliminary analyses of the OS endpoint based on the data cutoff for the ORR final analysis did not suggest a detriment in overall survival on the nivolumab arm of Trial CA209037 both in the subgroup of patients receiving treatment for a minimum of 6-months (nivolumab, n=120; chemotherapy, n=47) and in the all randomized subjects. Refer to the FDA Statistical BLA review for details.

Results of Trial CA209003, an open-label, multicenter, multidose, dose-escalation study of single-agent nivolumab across multiple tumor types provided supportive evidence of a treatment effect of nivolumab based on analyses of ORR and DOR. Trial CA209003 excluded patients who received prior anti-CTLA-4, anti-PD-1, or anti-PD-L1/L2 therapy. Of the 107 patients with advanced melanoma treated on this study, 87 received nivolumab doses at or below 3mg/kg every 2 weeks (0.1mg/kg, N=17; 0.3mg/kg, N=18; 1mg/kg, N=35 and 3mg/kg, N=17). The remaining 20 patients with melanoma received nivolumab at 10 mg/kg; these 20 patients were excluded from this supportive analysis.

Based on the raw datasets provided to FDA, among the 87 patients who received nivolumab doses  $\leq 3$  mg/kg, the median age was 61 years (range 29-85), 64% were male, 94% were white, 98% with metastatic disease at screening, and 28% had documented elevated LDH at baseline. Analysis of the datasets provided to FDA (data cutoff date of March 2013) demonstrated an ORR (investigator-assessed tumor measurements per RECIST 1.0) of 33.3% (95% CI: 23.6, 44.3), with a median DOR of 22.9 months (95% CI: 12.9 months, NR) in these 87 patients. Of the 29 patients with an objective response, the durations of response ranged from 4.2 to 26.6+ months. As described in the FDA Clinical Pharmacology BLA review and the FDA Clinical Review, a dose-response relationship was not evident across the dose range from 0.1 mg/kg to 10 mg/kg.

## 8. Safety

I agree with the overall conclusions of the primary FDA Clinical Reviewer for safety, Dr. Maitreyee Hazarika, regarding the safety data submitted in the BLA. I agree with Dr. Hazarika and Dr. Carolyn Yancey, Division of Risk Management, that a REMS is not required for this application. However, this application includes a Medication Guide to communicate the serious risks of nivolumab and to enhance its safe use.

The safety profile of nivolumab was primarily evaluated in Trial CA209037 as this was the only trial that included a control arm in an advanced melanoma population and that enrolled a population that previously received ipilimumab [refer to Section 7 of this review and the FDA Clinical Review for details of the trial design]. Of the 405 randomized patients in Trial CA209037, there were 268 patients who received nivolumab 3 mg/kg intravenously every 2 weeks and 102 patients who received investigator's choice chemotherapy, either dacarbazine 1000 mg/m<sup>2</sup> intravenously every 3 weeks (n=45) or the combination of carboplatin AUC 6 intravenously every 3 weeks plus paclitaxel 175 mg/m<sup>2</sup> intravenously every 3 weeks (n=57).

The median duration of exposure to nivolumab was 5.3 months (range 1 day to 13.8+ months). The data cutoff dates for the safety data in the original BLA submission was March 10, 2014, and in the safety update was July 29, 2014. The demographics and baseline characteristics of nivolumab-treated patients was nominally different in the safety population (n=268) compared with those described for the efficacy population (n=120). Based on FDA analyses of the Trial CA209037 datasets (DM.xpt, VS.xpt, SUPPMH.xpt, SUPPCM.xpt, ADSL.xpt, ADCMS.xpt), the demographics and baseline characteristics were similar between nivolumab-treated patients (n=268) and chemotherapy-treated patients (n=102) in the safety population: 66% male, median age 59.5 years, 98% white, baseline ECOG performance status 0 (59%) or 1 (41%), 74% with M1c stage disease, 73% with cutaneous melanoma, 11% with mucosal melanoma, 73% received two or more prior therapies for advanced or metastatic disease, and 18% had brain metastasis. However, there were more nivolumab-treated patients (51%) than chemotherapy-treated (38%) with elevated LDH at baseline.

The primary clinical reviewer of safety evaluated an extended safety databases consisting of datasets for an additional 306 patients with advanced solid tumors, including 107 patients with ipilimumab-naïve unresectable or metastatic melanoma, who received nivolumab at doses ranging from 0.1 mg/kg to 10 mg/kg. The primary clinical reviewer of safety also evaluated patient-level line listings and/or summary level tables of serious adverse events for an additional approximate 1200 patients who received single-agent nivolumab across the clinical development program—a database supplemented by patient narratives selected based on additional factors such as known class effects and requirement for management with corticosteroids.

The key safety findings are as follows (based on Trial CA209037 unless otherwise noted):

- Fatal adverse events of pneumonitis in a combined analysis of Trial CA209037 and Trial CA209003 occurred in 0.9% (5/574) of the patients: four patients with non-small cell lung cancer (NSCLC) and one patient with colorectal cancer. There were no cases of fatal pneumonitis in Trial CA209037 or in patients with unresectable or metastatic melanoma enrolled in Trial CA209003.

Of note, four of the five cases occurred early in the development of nivolumab prior to the development of a recommended management algorithm. In addition, the attribution of findings consistent with pneumonitis to drug in patients with NSCLC can be challenging based on the underlying manifestations attributed directly to disease and/or sequelae, concomitant medications (including post-study), and supportive care. Lastly, analysis of the extended database suggests that the incidence is decreasing.

Submission of a trial or trials evaluating nivolumab in patients with unresectable or metastatic melanoma are required to confirm the clinical benefit of nivolumab [refer to Section 13 of this review]. FDA review of these trials should clarify the incidence of fatal immune-mediated pneumonitis in the indicated population. This reviewer recommends inclusion of this adverse reaction in the Warnings and Precautions Section of labeling based on review of the individual cases and in accordance with FDA labeling guidances for adverse reactions.

- Serious adverse events occurring up to 100 days after the last dose of treatment were reported in 50.4% of nivolumab-treated patients and 30.4% of chemotherapy treated patients (incidence inclusive of *malignant neoplasm progression* and *disease progression* adverse events). Serious adverse events reported to occur in  $\geq 2\%$  of nivolumab-treated patients compared with chemotherapy-treated patients were malignant neoplasm progression (20.9% vs. 12.7%), metastatic melanoma (2.6% vs. 0), and back pain (2.2% vs. 2.0%).

Of note, in an analysis of the AE.xpt dataset for Trial CA209037, exclusion of *malignant neoplasm progression* and *disease progression* terms resulted in an incidence of serious adverse events of 41.4% (111/268) of nivolumab-treated patients and 26.5% (27/102) of chemotherapy-treated patients. In an analysis of serious adverse events (AE.xpt dataset) occurring up to 30 days after the last dose of treatment, SAEs were reported in 44% of nivolumab-treated patients and 21.6% of chemotherapy treated patients (inclusive of *malignant neoplasm progression* adverse events).

- Discontinuations due to adverse events occurred in 9.3% (25/268) of patients receiving nivolumab and 11.8% (12/102) of patients receiving chemotherapy. The most frequent ( $\geq 2\%$ ) adverse event leading to discontinuation in patients receiving nivolumab compared with patients receiving chemotherapy was malignant neoplasm progression (3.7% vs. 2.0%).
- Delays in nivolumab administration due to AEs occurred in 25.7% (69/268) of patients receiving nivolumab and 30.4% (31/102) of patients receiving chemotherapy. AEs leading to treatment delay in  $\geq 1\%$  of nivolumab-treated patients were dyspnea (2.6%), pneumonitis (1.5%), amylase increased (1.5%), lipase increased (1.5%), adrenal insufficiency (1.1%), abdominal pain (1.1%), arthralgia (1.1%), and headache (1.1%).
- Grade 3-4 adverse events occurred in 42.2% of patients receiving nivolumab and in 50% (51/102) of patients receiving chemotherapy. Common ( $\geq 2\%$ ) Grade 3-4 AEs in nivolumab-treated patients compared with chemotherapy-treated patients were malignant neoplasm progression (7.8% vs. 2.0%), anemia (4.9% vs. 8.8%), abdominal pain (3.4% vs. 1.0%), hyponatremia (2.6% vs. 0), and vomiting (2.2% vs. 2.0%).
- Common adverse reactions ( $\geq 20\%$ ) occurring up to 30 days after the last dose of nivolumab was a composite term of rash (21%).
- Immunogenicity data is discussed in Section 5 of this Review.

Immune-mediated adverse reactions (imAR) were of special interest for this application based on the mechanism of action of nivolumab and the safety profile of related FDA-approved products, the anti-PD-1 monoclonal antibody, pembrolizumab, and the anti-CTLA-4 monoclonal antibody, ipilimumab. Overall, 32.8% (88/268) of nivolumab-treated patients and 18% (18/102) of chemotherapy-treated patients received corticosteroids (systemic or topical) during the study. In total, 22.8% (61/268) and 14.2% (38/268) of nivolumab-treated patients and 13.7% (14/102) and 4.9% (5/102) of chemotherapy-treated patients received systemic corticosteroids and topical corticosteroids, respectively, for an AE. The Applicant's database did not link concomitant medications to specific AEs, thus manual review was required to evaluate use of corticosteroids and outcomes for specific AEs.

The FDA clinical review of safety identified the following clinically significant imARs of nivolumab, as reflected in recommended labeling: pneumonitis (3.4%), colitis (2.2%), hepatitis (1.1%), and nephritis and renal dysfunction (0.7%). Additional immune-mediated adverse reactions occurring in < 1% of patients in Trial CA209037 were pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis. Grade 1 or 2 hypothyroidism and Grade 1 or 2 hyperthyroidism were reported in 7.8% (21/268) and 3% (8/268) of patients receiving nivolumab, respectively. Analyses of the timing of onset of imARs occurring in Trial CA209037 were limited for most imARs based on the relatively few cases; however, labeling of nivolumab includes median time-to-onset where appropriate and/or the range of time-to-onset for descriptive purposes.

Additional clinically significant imARs were identified by the FDA clinical reviewer of safety based on use of extended safety database of approximately 1800 patients exposed to nivolumab (denominator inclusive of Trial CA209037 and Trial CA209003); these were hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome. Based on the mechanism of action of nivolumab, identification of additional imARs is expected during routine pharmacovigilance as well as analyses of randomized clinical trial data.

## **9. Advisory Committee Meeting**

The application was not referred to an Oncologic Drug Advisory Committee (ODAC) as the safety profile is acceptable for treatment of patients with unresectable or metastatic melanoma that is refractory to ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; this is not a first-in-class product; the primary efficacy outcome measures are acceptable and similar to those used for previously approved products granted accelerated approval in patients with unresectable or metastatic melanoma; the application did not raise significant public health questions on the role of nivolumab in the treatment of patients for this indication; and outside expertise from ODAC was not necessary because there were no controversial issues that would benefit from advisory committee discussion.

## **10. Pediatrics**

Nivolumab is exempt from the pediatric study requirements of the Pediatric Research Equity Act (PREA), i.e., to assess the safety and effectiveness of the product for the claimed indication(s) in pediatric patients, because FDA granted this product orphan designation for patients with Stage IIb to IV melanoma on January 23, 2013.

## **11. Other Relevant Regulatory Issues**

- **Application Integrity Policy (AIP):** No issues.
- **Financial Disclosures:** Refer to FDA Clinical review of this BLA

- **Other GCP Issues:** None
- **DSI Audits**

The Office of Scientific Investigations (OSI) inspected three clinical sites: Site #50 (David Minor, MD); Site #16 (Jeffrey Weber, MD); and Site # 28 (Sandra P. D'angelo, MD). OSI also inspected the CRO that performed the blinded independent central review (b) (4). A Form FDA 483 was issued to one clinical site (Site 50) for failure to perform the investigation in accordance with the signed statement of the investigator and the investigational plan and failure to report promptly to the Institutional Review Board (IRB) all unanticipated problems involving risk to human subjects. I agree with the conclusions of the FDA clinical reviewer of safety that the inspectional observations should not impact the overall integrity of the data used in the analyses of safety in Trial CA209037.

In addition, OSI expected a Form 483 to issue to the CRO, (b) (4). Although no major inspection observations were noted, there were procedural issues related to Charter compliance and documentation of training for one employee. The CRO failed to request site confirmation for the intent of exams performed outside the scheduled window for scans. In addition, there was no documented evidence to demonstrate that one employee was trained specifically for Study CA209037 to conduct image Quality assessments. The field investigator did not find evidence that the protocol deviations importantly impact data integrity. I agree with the conclusions of OSI that these observations should not importantly impact the primary endpoint data.

## 12. Labeling

- **Proprietary name:** In the FDA Proprietary Name Memorandum dated October 24, 2014, Dr. Otto Townsend, Division of Medication Error Prevention and Analysis (DMEPA), and Dr. Chi-Ming Tu, DMEPA, concluded that the proposed proprietary name, Opdivo, is acceptable.
- **OSE /Division of Medication Error Prevention and Analysis (DMEPA):** DMEPA concluded the carton and container labeling, as amended and submitted on November 3, 2014, are acceptable.
- **Office of Prescription Drug Promotion (OPDP):** OPDP participated in labeling discussions and provided recommendations. Please see memorandum from Dr. Nick Senior dated December 16, 2014, for labeling recommendations.
- **Patient Labeling:** The FDA Patient Labeling team participated in labeling discussions and provided recommendations. Refer to the FDA Patient Labeling BLA Review dated December 16, 2014, for labeling recommendations.
- **Maternal Health:** Participated in labeling discussions and provided recommendations to labeling consistent with the publication of the *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014), consisting of recommendations for Section 5.7 (Embryofetal toxicity), Section 8.1 (Pregnancy), Section 8.2 (Lactation), and Section 8.3 (Females and Males of Reproductive Potential).

### 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval (21 CFR part 601, subpart E)
- Risk Benefit Assessment

Patients with unresectable or metastatic melanoma who have progression of disease following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor have a serious and life-threatening disease with a high unmet medical need. Melanoma develops at a relatively early age which results in a substantial number of years of life lost per person<sup>8</sup>, and once metastatic carries a grim prognosis—the five year survival rate is historically less than 10% for patients.

In general, FDA-approved treatment options in use for treatment of metastatic melanoma are limited and include immunotherapy (interleukin-2, ipilimumab, pembrolizumab), chemotherapy (DTIC), and, if BRAF V600 mutation positive, BRAF inhibitors (vemurafenib, dabrafenib) and a MEK inhibitor (trametinib). Only ipilimumab and vemurafenib have been demonstrated in clinical studies to prolong overall survival compared with conventional therapy. Dacarbazine and interleukin-2 may be used in this setting but objective responses with either product are low (< 20%) and have not been studied in this treatment refractory population. Furthermore, treatment with interleukin-2 is associated with substantial on-treatment toxicity and is an appropriate therapeutic option only in a selected subgroup of patients. FDA recently granted accelerated approval to another anti-PD-1 monoclonal antibody, pembrolizumab (Keytruda), for the proposed indication. This approval was based on an ORR of 24% (95% CI: 15, 34) with prolonged durations of response in this treatment-refractory patient population.

The recommendation for approval of BLA 125554 (Opdivo) is primarily based on the results of Trial CA209037, which demonstrated a clinically relevant, but modest ORR of 31.7% (95% CI: 23.5, 40.8) with prolonged durations of response in the first 120 nivolumab-treated patients with treatment-refractory melanoma with a minimum follow-up of 6 months. Of the 38 nivolumab-treated patients with objective responses, 87% (33/38) of the responses were ongoing as of the data cutoff date (range 2.6+, 10+ months) and responses were ongoing for greater than 6 months in 13 of the 38 patients. Exploratory analyses demonstrated the antitumor activity of nivolumab was consistent across subgroups. Subgroup analyses of Trial CA209003 (i.e., melanoma subpopulation) were supportive of the magnitude of ORR and durability of objective responses observed in an advanced melanoma population.

The primary safety risks of nivolumab identified in the 268 patients with melanoma in Trial CA209037 are immune-mediated adverse reactions (imAR), a finding that is consistent with the mechanism of action of nivolumab and with the safety profiles of similar FDA-approved

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<sup>8</sup> Ekwueme, DU, GP Guy, C Li, SH Rim, P Parelkar et al., 2011, The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006, J Am Acad Dermatol, 65 (5 Suppl 1):S133-43.

products—the anti-PD-1 monoclonal antibody, pembrolizumab, and the anti-CTLA-4 monoclonal antibody, ipilimumab. The most serious risk with nivolumab appears to be pneumonitis (3.4% all Grades), with fatal cases occurring in 0.9% (5/574) of patients treated with nivolumab at a range of doses from 1 mg/kg to 10 mg/kg. Of note, the incidence of fatal pneumonitis appeared to decrease in clinical trials following recognition of pneumonitis as an adverse reaction and implementation of management algorithms, including nivolumab dose delays or discontinuation. In addition to pneumonitis, the FDA clinical review of safety identified the following clinically significant imARs: colitis (2.2%), hepatitis (1.1%), and nephritis and renal dysfunction (0.7%). Grade 1 or 2 hypothyroidism and Grade 1 or 2 hyperthyroidism were reported in 7.8% and 3% of patients receiving nivolumab, respectively. In general, these cases were managed without corticosteroids and were controlled with hormone replacement or medical management. Additional imARs with nivolumab treatment occurring in < 1% of patients in Trial CA209037 were pancreatitis, uveitis, demyelination, autoimmune neuropathy, adrenal insufficiency, and facial and abducens nerve paresis. Across the development program of nivolumab, additional clinically significant imARs were hypophysitis, diabetic ketoacidosis, hypopituitarism, Guillain-Barré syndrome, and myasthenic syndrome.

Nine percent of nivolumab-treated patients experienced adverse events (AE) leading to treatment withdrawal. Delays in nivolumab treatment for AEs occurred in 26% of patients; common ( $\geq 1\%$ ) AEs leading to treatment delay were dyspnea (2.6%), pneumonitis (1.5%), amylase increased (1.5%), lipase increased (1.5%), adrenal insufficiency (1.1%), abdominal pain (1.1%), arthralgia (1.1%), and headache (1.1%). The most frequent ( $\geq 20\%$ ) adverse reaction of nivolumab was rash (21%).

The risk-benefit assessment of nivolumab is favorable for the treatment of patients with unresectable or metastatic melanoma and progression of disease following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor—a treatment refractory population with no satisfactory available therapy. In this treatment refractory population, nivolumab at a dose of 3 mg/kg administered once every 2 weeks demonstrated an objective response rate with durations of response that are of sufficient magnitude—31.7% ORR with ongoing responses in 33 of the 38 (87%) responding patients ranging from 2.6+ to 10+ months, including 13 patients with response durations of greater than 6 months—to be considered reasonably likely to predict clinical benefit. In general, immune-mediated adverse reactions, the major safety risk with nivolumab, were manageable with high-dose systemic corticosteroids followed by a corticosteroid taper. Prescribers are familiar with management of imARs based on the similar safety profiles of another anti-PD-1 monoclonal antibody, pembrolizumab, that received accelerated approval in September 2014, and of ipilimumab, an anti-CTLA monoclonal antibody which received regular approval in 2011. It is uncertain whether the prolonged objective responses observed with nivolumab will translate into outcomes of clinical benefit, e.g., an improvement in survival or irreversible morbidity, and, therefore, as a condition of accelerated approval the Applicant must verify and describe the benefit of nivolumab.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I agree with the recommendations of the BLA review team, including DRISK, that a REMS is not required to ensure safe use of nivolumab.

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirement is recommended to fulfill the requirements under 21 CFR part 601, subpart E to verify and describe the clinical benefit of nivolumab:

1. 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.

CMC recommended the following postmarketing commitments:

1. To re-evaluate nivolumab drug substance lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.
2. To re-evaluate nivolumab drug product lot release and stability specifications after 30 lots have been manufactured using the commercial manufacturing process. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.
3. To develop and validate a process-specific host cell protein (HCP) assay that has improved sensitivity and capability to detect a greater range of potential HCPs compared to the current assay and to implement this assay in the nivolumab drug substance release program. The analytical procedure, validation report, proposed specification acceptance criterion, and data used to set the proposed acceptance criterion will be provided in the final study report.
4. To optimize and re-validate a non-reduced CE-SDS method that has improved reproducibility. The analytical procedure, validation report, any proposed changes to specification acceptance criteria, and the data used to set the proposed acceptance criteria will be provided in the final study report.
5. Re-evaluate and tighten the endotoxin limits for the following in-process samples:  
[REDACTED] (b) (4)  
[REDACTED]. Re-evaluate and tighten the endotoxin limits for the following additional samples: [REDACTED] (b) (4)  
[REDACTED]

Table Appendix A: FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma

FDA Approved Drug <sup>1</sup>	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
DTIC (dacarbazine) <sup>2</sup>	1975	Single-arm	ORR	ORR of 5-20%
Proleukin (interleukin-2) <sup>2</sup>	1998	Multicenter single-arm	ORR	ORR 16% (CR 6%); DOR CR: 59+m (3 to 122+ m) CR or PR: 59+ m (1 to 22+m)
Yervoy (ipilimumab) <sup>2</sup>	2011	Multicenter, randomized, blinded, active-controlled three-arm	OS ORR	<b><u>Ipi vs. gp100:</u></b> OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 m BORR: 10.9% vs. 1.5% mDOR: not reached in either arm  <b><u>Ipi+gp100 vs. gp100:</u></b> OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 m BORR: 5.7% vs. 1.5% mDOR: 11.5 m vs. NR
Zelboraf <sup>3</sup> (vemurafenib)	2011	Randomized, open-label active-controlled, two-arm	OS PFS ORR	<b><u>Vemurafenib vs. DTIC</u></b> mOS: NR vs. 7.9 m HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 vs. 1.6 m HR: 0.26 (95% CI: 0.20, 0.33) cORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%
Tafinlar <sup>3</sup> (dabrafenib)	2013	Randomized, open-label active-controlled, two-arm	PFS ORR	<b><u>Dabrafenib vs. Dacarbazine</u></b> mPFS: 5.1 vs. 2.7 m HR: 0.33 (95% CI: 0.20, 0.54) cORR: Dabrafenib: 52% (95% CI: 44%, 59%) CR 3% PR 48% Dacarbazine: 17% (95% CI: 9%, 29%) CR 0% PR 17%

FDA Approved Drug <sup>1</sup>	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
Mekinist <sup>4</sup> (trametinib)	2013	Randomized, open-label active-controlled, two arm	PFS ORR	<b>Trametinib vs. Chemotherapy</b> mPFS: 4.8 vs. 1.5 m HR: 0.47 (95% CI: 0.34, 0.65) cORR: Trametinib: 22% (95% CI: 17%, 28%) CR 2% PR 20% Chemotherapy: 8% (95% CI: 4%, 15%) CR 0% PR 9%
Tafinlar and Mekinist <sup>5</sup> (dabrafenib and trametinib)	2014 <sup>6</sup>	Randomized, open-label, active-controlled, two arm portion of dose-escalation study	ORR	<b>Dabrafenib plus Trametinib vs. single-agent Dabrafenib</b> ORR 76% vs. 54% mDOR 10.5m vs. 5.6m mPFS: 9.4m vs. 5.8m HR: 0.39 (95% CI: 0.25, 0.62)
Keytruda (pembrolizumab) <sup>7</sup>	2014 <sup>8</sup>	Single-arm analysis (dose-comparison)	ORR	ORR of 24% (95% CI: 15, 34) DOR: range 1.4+ to 8.5+ months 86% of responses ongoing, 8 patients With responses ongoing for > 6 months

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Source: Proleukin (USPI); Yervoy (USPI); Zelboraf (USPI); Dacarbazine (USPI); Tafinlar (USPI); Mekinist (USPI).

Abbreviations in Table: m, months; BORR, best overall response rate; CR, complete response; cORR, confirmed objective response rate; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; +, response is ongoing.

<sup>1</sup> Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.

<sup>2</sup> BRAF V600 mutation status unknown.

<sup>3</sup> Patient selection based on BRAF V600E mutation-positive tumors.

<sup>4</sup> Patient selection based on BRAF V600E or V600K mutation-positive tumors

<sup>5</sup> Patient selection based on BRAF V600E, V600K, or V600D mutation-positive tumors

<sup>6</sup> Accelerated approval as per 21 CFR 314.510 of subpart H

<sup>7</sup> Patient's refractory to ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

<sup>8</sup> Accelerated approval as per 21 CFR 601.41

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARC R THEORET  
12/22/2014