

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125554Orig1s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: December 4, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Acting Team Leader: Naomi Redd, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of nivolumab for injection outweigh the risks

Drug Name: OPDIVO (nivolumab) Injection, for Intravenous Injection

Therapeutic Class: Programmed Death Receptor-1 Inhibitor

Dosage, Form, Strength: 3 mg/kg administered intravenously over 60 minutes every 2 weeks; dosage form and strengths: 40 mg/ 4 mL (10 mg/mL) and 100 mg/10 mL (10 mg/mL)

Office of New Drugs: Division of Oncology Products - 2

Application Type/Number: BLA 125-554, Original 00 received on July 30, 2014

Applicant: Bristol-Myers Squibb (BMS) Company

OSE RCM #: 2014-1847 Risk Management Plan Review
2014-1804 NME PDUFA V Program, MASTER RECORD

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APPENDIX

EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for nivolumab (Opdivo), a new molecular entity (NME), proposed for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.¹ This biologic license application (BLA) 125-554 submission includes a proposed risk management plan (RMP) that does not include a REMS.

The DRISK and the Division of Oncology Products (DOP-2) concurred that nivolumab does not require a REMS to ensure that the benefits outweigh the serious risks of immune-mediated (IM) skin rash, colitis, endocrine events (including thyroid dysfunction, adrenal insufficiency and hypophysitis), hepatotoxicity, pneumonitis, and nephritis and/or renal failure. The DOP-2 and the DRISK concluded that oncology healthcare providers are informed on similar severe and fatal immune-mediated risks based use of ipilimumab (IPI), approved on March 25, 2011, for the treatment of unresectable or metastatic melanoma. This same rationale was applied by the DRISK and the DOP-2 to not require a REMS for Keytruda (pembrolizumab), approved September 4, 2014.²

The applicant proposed non-REMS materials in the RMP to inform oncologists and oncology patients on the serious risks associated with use of nivolumab. The DOP-2 and the DRISK concluded that the non-REMS materials, that are not required, may be informative to oncologists and oncology patients on the serious risks associated with use of nivolumab. These proposed materials are considered promotional will be reviewed by the Office of Prescription and Drug Promotion (OPDP).

The prescription drug user fee act (PDUFA) Goal Date is March 30, 2015. The internal action date is December 19, 2014.

1 INTRODUCTION

The original Biologic License Application (BLA) 125-554 for nivolumab was received by the DOP-2 on July 30, 2014. The clinical development program for nivolumab is under Investigational New Drug (IND) application 115-195 for Nivolumab [BMS-936558, MDX-1106, or ONO-4538] in Advanced [Unresectable or Metastatic] Melanoma in Patients Progressing Post Anti-Cytotoxic T-lymphocyte Antigen-4 [CTLA-4] Therapy. Nivolumab has an expanded access program (EAP) as monotherapy in non-

¹ BRAF is a human gene that makes a protein called B-Raf, also referred to as a proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. The BRAF protein is involved in sending signals inside cells which are involved in directing cell growth. This protein was shown to be faulty (mutated in some human cancers). Ref: DH Bignell et al. Mutations of the BRAF Gene in Human Cancer. Nature, 2002, Jun 27; 417 (6892):949-54.

² Keytruda (pembrolizumab) was approved September 4, 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Keytruda is associated with similar severe or life-threatening immune-mediated risks (no Boxed Warning in labeling) as reported with nivolumab.

small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma (RCC), and an EAP as in-combination therapy with IPI for melanoma. See **Section 2.4 Regulatory History**, in this review, for milestones under this IND.

2 BACKGROUND

2.1 PRODUCT BACKGROUND

As explained by the applicant, “nivolumab (BMS-936558, MDX-1106, ONO-4538) is a programmed death-1(PD-1) inhibitor that regulates T-cell activity to control tumor-specific inhibition of T-cells through programmed death ligands-1 and -2 (PD-L1 and PD-L2).”³ Nivolumab is considered a PD-1 immune checkpoint inhibitor. This mechanism of action, through PD-1 and PD-2 ligands, results in inhibition of T-cell proliferation, survival, and cytokine secretion.¹ Nivolumab is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that promotes *in vitro* T-cell responses through dual ligand blockade of PD-1 and PD-2, and does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC).³

Expression of PD-L1 and PD-L2 by malignant cells or other cells allows different tumor types to evade immune-mediated destruction. Nivolumab is proposed to restore T-cell activity either by preventing inactivation or by reactivating T-cells to mount a direct T-cell immune attack against tumor cells, including an increase in cytotoxic CD8 T-cells in the tumor, without measureable increase in activated circulating T-cells peripheral to the tumor.³

Nivolumab is proposed by the applicant as pregnancy category (b) (4). The applicant completed an embryo fetal study in monkeys and demonstrated that the risk to pregnancy is fetal and/or neonatal death. Per the pharmacology/toxicology reviewer, these results are consistent with the mechanism of action identified in mice, suggesting that PD-1 is involved in maintaining tolerance to the fetal allograft. Based on this information, the Agency recommends pregnancy category (b) (4) for nivolumab, consistent with labeling (Section 8.1) for pembrolizumab as pregnancy category D.

2.2 PROPOSED FORMULATION AND DOSAGE

The proposed, to-be-marketed formulation and strength for nivolumab is 10 mg/mL to be prepared as an infusion with the final concentration ranging from 1 to 10 mg/mL. There are two proposed nivolumab dosage strengths: 40 mg/mL (10 mg/mL) and 100 mg/mL (10 mg/mL). The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous (IV) infusion over 60 minutes every 2 weeks. This product does not contain a preservative.

2.3 DISEASE CONDITION - MALIGNANT MELANOMA

Melanoma is an aggressive malignancy of melanocytes: pigment producing cells that originate from the neural crest and migrate to the skin, meninges, mucous membranes,

³ BLA 125-554 Nivolumab, Global Submit (GS), Module 2.2 Common Technical Document Summaries (CTDS), page 10 of 48

upper esophagus, and eyes.⁴ Melanocytes in each of these locations have the potential for malignant transformation. In the United States (US), nearly 69,000 individuals were expected to develop melanoma and approximately 9,000 were expected to die in 2010. Although the overall incidence and mortality have increased over the last decades, the mortality rates for younger patients have flattened whereas those rates for individuals over age 65 years have continued to increase.⁴

It is predominantly a malignancy of white-skinned people (98% of cases), and the incidence correlates with latitude of residence, providing strong evidence for the role of sun exposure. Men are affected slightly more than women (1.3:1), and the median age at diagnosis is the late fifties. Dark-skinned populations also develop melanoma, albeit at rates 10 to 20 times lower than in whites. Cutaneous melanomas in these populations are diagnosed more often at a higher stage, and patients tend to have worse outcomes.⁴

The strongest two risk factors for melanoma are the presence of multiple benign or atypical nevi and a family or personal history of melanoma. The presence of melanocytic nevi, common or dysplastic is a marker for increased risk of melanoma.⁴

When a patient with a history of melanoma develops signs or symptoms of recurrent disease, he or she should undergo restaging.⁴ Restaging includes an MRI of the brain and total-body PET/CT scans of the chest, abdomen, and pelvis. Distant metastases (stage IV), which may involve any organ, commonly include skin and lymph node metastases as well as visceral, bone, or brain metastases. Metastatic melanoma is generally incurable, and median survival ranges from 6 to 15 months, depending on the organ involved. The prognosis is better for skin and subcutaneous metastases (M1a) than for lung (M1b) or other visceral metastases (M1c). An elevated serum lactate dehydrogenase (LDH) in a patient with metastatic disease is a poor prognostic factor and puts the patient in stage M1c, regardless of the site of the metastases.⁴

2.4 ARMAMENTARIUM OF THERAPY - TREATMENT OF MALIGNANT MELANOMA

The FDA-approved chemotherapy for melanoma includes two alkylating agents: dacarbazine (DTIC), administered by IV infusion, and Temozolomide (Temodar, TMZ) administered as an oral capsule.⁵ There is no one single standard-of-care or preferred treatment since approval of IPI (Yervoy) in March 2011 for the treatment of unresectable or metastatic melanoma.⁵ Approved products with similar indications are:⁶

- Vemurafenib (Zelboraf), approved by the FDA August 2011, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

⁴ 18th Edition, Harrison's Principles of Internal Medicine by Longo DL, Fauci AS, Kasper DL, Hasuer SL, Jameson JL, and Loscalzo J. Chapter 87 by Urba WJ, Washington CV, Nadiminiti H.: Cancer of the Skin, pages 723 to 729.

⁵ Clinical Summary Document - Clinical Summary of Studies CA184-338 and CA 184-143 (IMAGE), Bristol-Myers Squibb Company; 2014.document control Number 930081961

⁶ BLA 125-554 OPDIVO (nivolumab), GS, Module 2.5, Clinical Overview, Table 1.2.4-1, page 9 of 48

- Dabrafenib (Tafinlar), approved by the FDA January 2014, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
- Trametinib (Mekinist), approved by the FDA January 2014, is indicated as a single agent and, in combination with dabrafenib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.
- Pembrolizumab (Keytruda), cited earlier in this review, is approved for treatment of patients with unresectable or metastatic melanoma and disease progression following IPI and, if BRAF V600 mutation positive, a BRAF inhibitor.

Cytotoxic chemotherapy remains a treatment option if a patient progresses on one or more of the new agents.⁷

Products used to treat melanoma off-label include cisplatin and carboplatin, both alkylating agents, and the taxanes [paclitaxel (Taxol) and docetaxel (Taxotere)]. The taxane mechanism of action is to block cell growth by stopping mitosis.

Although limited in efficacy, single-agent DTIC remains the standard treatment because drug combinations have never been shown to improve overall survival.³ Temozolomide, which shares an active metabolite with DTIC, has also been used to treat malignant melanoma because of its ease of oral administration, tolerance, and penetration across the blood-brain barrier.³

2.5 REGULATORY HISTORY

The regulatory history specific to BLA 125-554 for nivolumab follows:

- June 13, 2012: The sponsor (BMS) submitted the new development program for nivolumab for the treatment of metastatic melanoma (Protocol CA209038 entitled, “An Exploratory Study of the Biologic Effects of BMS-936558 (anti-PD-1 monoclonal antibody) Treatment of Patients with Advanced Melanoma (unresectable or metastatic)” under IND 115-195. IND 115-195 was initiated as an administrative split from the original IND 100-052 for nivolumab that includes the Chemistry, Manufacturing and Controls (CMC), non-clinical information for nivolumab, and dose-finding/tolerability studies.
- October 4, 2012: The Agency granted Fast Track Designation for nivolumab in patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival (OS) over available therapies.
- October 17, 2012: Under IND 115-195, the sponsor submitted Protocol CA209-037, “A Randomized (R), Open-label (OL), Phase (P) 3 trial of BMS 936558 versus (vs) the Investigator’s Choice in patients with Advanced (unresectable or metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy.”

⁷ NCCN Guidelines Melanoma Version 2, 2014

- October 22, 2012: Under IND 115-195, the sponsor submitted Protocol CA209-066 entitled, “A P3, R, Double-blind (DB), Study of Nivolumab vs Dacarbazine in Patients with Previously Untreated Unresectable or Metastatic Melanoma.” It was clarified in the IND submission that this study would only be conducted at non-US sites.
- January 13, 2013: The Agency granted Orphan Drug Designation for nivolumab for the treatment of Stage IIb to Stage IV malignant melanoma in the US.
- January 16, 2014: The Agency advised the sponsor to de-couple the timing of the analysis of the co-primary efficacy endpoints, objective response rate (ORR) and OS in Study CA209037.
- July 9, 2014: Pre-BLA Meeting (multidiscipline) discussion included agreement that the primary analysis of ORR will be performed when approximately 180 treated patients have a minimum follow-up of 6 months. One formal OS interim analysis will be conducted when at least 169 deaths have been observed. There was one sponsor question in regard to the proposed risk management strategy:
 - Question: Based on the preliminary study results for CA209-037 and safety profile from the additional nivolumab studies, does FDA agree with the current proposed risk management strategy, which includes a Medication Guide that will be part of the US product labeling and does not propose/include a risk evaluation and mitigation strategy (REMS)?
 - FDA Response: Since additional information regarding risks and safe product use may emerge during the review of the actual trial results in the BLA, it is premature to determine whether a REMS will be required. However, based on the available safety information in the pre-meeting briefing package, we agree that submission of a REMS will not be required for filing of the BLA.
- July 30, 2014: The applicant submitted the original BLA 125-554 OPDIVO (nivolumab) proposed for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status.
- September 11, 2014: The Agency granted Breakthrough Designation for nivolumab for the treatment of advanced (unresectable or metastatic) melanoma in patients whose disease has progressed on or after anti-CTLA-4 therapy, and for the treatment of advanced (unresectable or metastatic), BRAF V600 mutation-positive melanoma in patients whose disease has progressed on or after both BRAF inhibitor (BRAFi) and anti-CTLA-4 therapy for the treatment of Stage IIb to Stage IV melanoma in the US.
- October 16, 2014: The DRISK, the Division of Pharmacovigilance (DPV), and the DOP-2 Clinical Team held an *internal meeting* to discuss the applicant’s RMP that includes a Failure Modes and Effects Analysis (FEMA), proposed non-REMS materials to inform oncology providers and oncology patients on the serious risks with use of nivolumab, reported serious risks with use of nivolumab, and whether a REMS needs to be required, if nivolumab should be approved. As cited in the **Executive Summary** of this review, the DOP-2 and the DRISK concurred that a REMS will not be needed to ensure that the benefits of nivolumab outweigh the risks.

The DOP-2 concluded that the proposed non-REMS materials will be useful to inform oncologists and oncology patients on the serious immune-mediated risks with use of nivolumab. The DRISK clarified that these non-REMS materials are considered promotional and will, therefore, be reviewed by the OPDP.

- October 24, 2014: The Division of Medication Error Prevention and Analysis accepted the proposed proprietary name, OPDIVO for nivolumab.
- October 30, 2014: The DOP-2 held the Mid-Cycle Meeting for nivolumab. This reviewer briefly summarized the applicant's RMP/FEMA and shared that the DOP-2 and DRISK concurred that a REMS for OPDIVO will not be required for nivolumab. See the **Executive Summary** and **Discussion**, in this review, for comment on the rationale for this decision.
- November 13, 2014: The DOP-2 informed the applicant that the proposed non-REMS materials are considered promotional and will need to be submitted to the OPDP for review.

2.2 Materials Reviewed

- July 30, 2014: Original BLA 125-554 OPDIVO (nivolumab) Injection, proposed for the treatment of patients with unresectable or metastatic melanoma in patients previously treated with ipilimumab, regardless of BRAF status. This BLA includes a RMP (Module 1.16 Risk Management Plan).
- October 22, 2014: Label and Labeling Review by Otto L. Townsend, Pharm. D., DMEPA and Chi-Ming (Alice) Tu, Pharm. D., Team Leader, DMEPA
- October 28, 2014: BLA 125-554 OPDIVO (nivolumab), 90-Day Safety Update Report.
- October 30, 2014: BLA 1250554 OPDIVO (nivolumab) Mid-Cycle Review slides by Meredith Chuk, MD, Clinical Efficacy Reviewer, DOP-2, and Maitreyee Hazarika, Pharm. D., Clinical Safety Reviewer, DOP-2.
- November 3, 2014: Mid-Cycle Communication Meeting Minutes.
- November 26, 2014: The DOP-2 revisions to substantially complete proposed nivolumab labeling.
- *December 2014: Pending* Clinical Pharmacology Review by Xianhua (Walt) Cao, Pharm. D., Hongshan Li, Pharm. D., Office of Clinical Pharmacology (OCP) Reviewers and Liang Zhao, Pharm. D. and Hong Zhao, Pharm. D. Team Leaders, OCP
- *December 2014: Pending* Clinical Efficacy Review for Nivolumab written by Meredith Chuk, M. D. DOP-2
- *December 2014: Pending* Clinical Safety Review for Nivolumab written by Maitreyee Hazarika, Pharm.D.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The efficacy and safety of nivolumab is derived from two P 3 studies (CA209037/**study CA-037** and CA209066/**study CA-066**), and one P1b study (MDX1106-03 (also known as study CA-209003)/**study MDX-03**) that includes a large expansion cohort in melanoma patients which provides supportive evidence of efficacy and safety for this BLA.

Study CA-037 is a P3, R, OL study of nivolumab (3 mg/kg every 2 weeks (Q2W) vs the investigator’s (inv.) choice (2:1, dacarbazine or carboplatin and paclitaxel) in patients with advanced (unresectable or metastatic) melanoma who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after treatment with a BRAF inhibitor, in addition to anti-CTLA-4-therapy. Study CA-037 is ongoing.

A total of 405 patients were randomized (nivolumab, 272 patients; inv. choice, 133 patients). See **Table 1** per the applicant [BLA 125-554 Nivolumab, GS, Module 2 CTDS, Section 2.5 Clinical Overview] and the Mid-Cycle Clinical Efficacy slides with details on the patients in study CA-037.

Table 1. Patient Populations in Pivotal P3 Study CA-037

Analyses Population	Nivolumab	Investigator’s Choice
All Randomized Patients	272	133
All Treated Population	268	102
ORR Population – all randomized patients with at least 6 months of follow-up	122	60
Treated patients among ORR population	120*	47
*Primary endpoint analysis population.		

The primary efficacy analysis (ORR) was performed on a total of 120 nivolumab-treated patients. The secondary endpoints included progression-free survival (PFS), PD-L1 expression as a predictive biomarker for ORR and OS and health-related quality of life measures. See the Clinical Efficacy Review by Meredith Chuk, MD for details on discontinuations/drop-outs as applies to efficacy data.

Study MDX-03 is a supportive P1b (expansion cohort), OL, multiple-ascending dose study (0.1, 0.3, 1, 3, and 10 mg/kg Q2W) to evaluate the safety and efficacy of nivolumab in patients with prior-treated solid tumor malignancies. A total of 107 patients were enrolled in study MDX-03 (this study population included patients with at least 1 prior systemic therapy; IPI was not allowed).

Tumor responses were centrally assessed by the applicant using the RECIST v1.0 based on tumor measurements collected by the clinical investigators. The primary efficacy endpoint in study MDX-03 was ORR.

Study Population and Demographics

The study populations across study A-037 and study MDX-03 crossed 90 different sites in 14 countries (US, Austria, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland and the United Kingdom) and baseline characteristics

among the nivolumab and the inv. choice treated patients were comparable. In study CA-037, patients had significant disease burden with at least 2 sites of disease. The most common organ sites were: lung and liver. In study CA-037 and study MDX-03, respectively, brain metastases (20% vs 14%) and elevated lactate dehydrogenase (LDH) > upper limit of normal (ULN) (51% vs 35%) were noted to be poor prognostic predictors indicating a higher disease burden.

In study MDX-03, the majority (62%) of melanoma patients had received 2 or more prior lines of therapy. In addition to anti-CTLA-4 and BRAF inhibitors, the most common prior therapy in study CA-037 was dacarbazine (28%) followed by temozolomide (12%). In study CA-037, the majority of patients had Stage IV disease and 76% had M1c metastatic stage at baseline (BL) and 67% had 2 or more disease/organ sites.

Demographics across study CA-037 and MDX-03, respectively, were comparable: the majority of patients were Caucasian (98% and 95%), male (65% and 67%), and the median age was 58 years and 61 years. See the Clinical Efficacy Review by Meredith Chuk, MD, for additional details.

Patient Disposition

The most common reason for stopping treatment was disease progression (43% in the nivolumab group vs. 61% in the inv. choice group). See the Clinical Efficacy Review by Meredith Chuk, M. D. for details of other events reported in the patient disposition as applies to the efficacy analyses.

Efficacy Results

The applicant is seeking accelerated approval based on data from one interim/ongoing P3 study CA-037 co-primary endpoint of ORR [non-comparative point estimate of an independent radiology review committee (IRRC) using Response Evaluation Criteria in Solid Tumors [(RECIST) v1.1], assessed in the first 120 patients treated with nivolumab with at least 6 months follow-up. A subsequent application to support potential conversion to regular approval will be based on study CA-037 co-primary endpoint of OS.

Study CA-037 and MDX-03

Nivolumab demonstrated durable anti-tumor activity at 3 mg/kg Q2W in refractory patients with unresectable or metastatic melanoma in study CA-037 by an IRRC-assessed ORR of 31.7% (95% CI: 23.5, 40.8) based on analysis of the first 120 nivolumab-treated patients with at least 6 months of follow-up. The lower bound of 23.5% observed in study CA-037 with nivolumab was consistent with the ORR observed in study MDX-03 (30.8% [95% CI: 22.3, 40.5] across all dose levels, and 41.2% [95% CI: 18.4, 67.1] at 3 mg/kg Q2W). The ORR in the inv. choice treatment-arm in study CA-037 was 10.6% [95% CI: 3.5, 23.1].

As confirmed with the Clinical Efficacy Reviewer, at the time of the study CA-037 database lock (date March 14, 2014), the median duration of response (DOR) among the responders demonstrated a range of 1.4+ months to 10.0+ months, suggesting potential for nivolumab to induce longer term durable responses. The median DOR for the investigator's choice demonstrated 3.6 months with a range of 1.3+, 3.5 months. Study

MDX-03 suggested a similar trend by the prolonged DOR. See the Clinical Efficacy Review by Meredith Chuk, M. D. for details on these efficacy results.

Subgroup analyses in study CA-037 were supportive of the primary efficacy results for nivolumab (see **Tables 2** and **3** below). The Clinical Pharmacology Reviewers, Xianhua (Walt) Cao, Pharm. D. and Hongshan Li, Pharm. D. reported that ORR decreased with increasing tumor burden. There appears to be a potential positive trend for ORR and PD-1 positivity in these subgroup analyses.

Table 2. Subgroup Analysis: PD-1 Expression

		Nivolumab	Investigator's Choice
PD-1 Status	Total N = 167	ORR (95% CI)	ORR (95% CI)
Positive	77	43.6 (30.3, 57.7)	9.1 (1.1, 29.2)
Negative	87	20.3 (11.3, 32.2)	13 (2.8, 33.6)
Indeterminate	3	100 (2.5, 100)	0 (0, 84.2)
Per Mid-Cycle Clinical Efficacy slides per the Clinical Efficacy Reviewer (dated October 30, 2014)			

Table 3. Subgroup Analysis: BRAF Mutation

		Nivolumab	Investigator's Choice
BRAF Status	Total N = 167	ORR (95% CI)	ORR (95% CI)
Mutant	37	23.1 (9, 43.6)	9.1 (0.2, 41.3)
Wild Type	130	34 (24.6, 44.5)	11.1 (3.1, 26.1)
Per Mid-Cycle Clinical Efficacy slides per Clinical Efficacy Reviewer (dated October 30, 2014)			

3.1 CLINICAL SAFETY

Across all clinical studies with nivolumab, there were a total of 1,524 exposed patients. The primary clinical safety profile for nivolumab is based on safety data collected from 268 patients with advanced melanoma treated with nivolumab 3 mg Q2W monotherapy in the study CA-037. Clinical safety with nivolumab is compared to safety data on a total of 102 patients treated with the inv. choice of other therapies.

Extent of Exposure

The median duration of nivolumab therapy was longer (5.3 months) compared with the inv. choice (2 months [dacarbazine and 2.9 months with carboplatin and paclitaxel]). The mean number of nivolumab doses received was 9.4 [standard deviation (SD) 6.70] compared with dacarbazine (n = 45 patients; 3.7 mean doses (2.21 SD); carboplatin (n = 57 patients, 4.6 mean doses (2.18 SD); and paclitaxel (n = 57 patients, 4.6 mean doses (2.18 SD)).⁸ See the **Appendix**, to this review, for **Figure 1.2.2-1**, Kaplan-Meier Plot of

⁸ See BLA 125-554 Nivolumab, GS, Module 2.7.4 Summary of Clinical Safety, Table 1.2.2-1, page 22 of 139.

Duration of Study Therapy - All Treated, that demonstrates the greater exposure to nivolumab compared to other therapies employed in study CA-037.

3.1.1 Deaths

There were a total of 67 deaths (25%) nivolumab treatment and 24 deaths (24%) inv. choice treatment and, as expected, the majority of deaths were attributed to disease progression [63 deaths (24%) nivolumab; and 23 deaths (23%) with inv. choice treatment].

There were a total of 5 deaths for reasons other than disease progression: 4 patients treated with nivolumab and 1 patient treated with the inv. choice. Among the 4 patients treated with nivolumab, causality was cited (for each patient) as “unknown”; cardiopulmonary arrest; sudden death due to probable pulmonary embolism/pneumonia (per autopsy); and multi-organ failure.

There were 2 other deaths reported as Grade 5 adverse events (AEs) attributed to disease progression. On internal adjudication by the Clinical Safety Reviewer, 1 patient’s death was attributed to cardiac failure and a second patient’s death was attributed to pneumonia. See the Clinical Safety Review for additional details on each of the above cited deaths (deaths reported through 30 days and 100 days from the last dose).

3.1.2 Drop-Outs and/or Discontinuations

As cited earlier in this review, the most common reason for treatment discontinuation was disease progression. **Table 4** includes reasons for treatment discontinuations across the nivolumab treatment group and the inv. choice treatment group (as presented at the Mid-Cycle Meeting by the Clinical Safety Reviewer). Per the Clinical Safety Reviewer, treatment discontinuations due to AEs were 9% with nivolumab compared to 12% with the inv. choice treatment. Treatment interruptions due to AEs were 37% with nivolumab treatment compared with 65% with inv. choice treatment.

Table 4. Treatment Discontinuations

Category	Nivolumab N=268; n (%)	Inv. Choice N= 102; n (%)
Total Discontinued	139 (52)	84 (82)
Disease progression	116 (43)	62 (61)
Study drug toxicity	7 (3)	7 (7)
Death	6 (2)	0
Withdrew consent	2 (1)	5 (1)
Lost to follow-up	0	0

Ref: Table is from the Mid-Cycle slides by the Clinical Safety Reviewer.

3.1.3 Serious and Severe Adverse Events

The non-fatal serious AEs (SAEs) were reported up to 30 days after the last dose of study therapy, regardless of causality, were higher in the nivolumab group (118 patients, 44%) compared to the inv. choice group (22 patients, 21.6%). In the nivolumab group, the

majority of SAEs occurred in $\leq 2\%$ of patients except for malignant neoplasm progression which occurred in 10.4% of patients. In the inv. choice group, the most frequently reported SAEs $\geq 2\%$ were malignant neoplasm progression (3.9%), dyspnea (2.9%), vomiting, pyrexia, fatigue, back pain, anemia, and acute renal failure (each 2.0%). The SAEs that resulted in a fatality were reported in **Section 3.1.1**, in this review.

Grade 3 to 4 AEs were reported as 29% of nivolumab treated patients and 16% of patients in the inv. choice group. (See **Table 6**, Serious Adverse Events in $\geq 1\%$ of patients in the Nivolumab group).

Table 6 Serious Adverse Events ($\geq 1\%$) Nivolumab versus Inv. Choice

Preferred Term	Nivolumab, N = 268		Inv. Choice, N = 102	
	Grade 3 to 4	Grade 3 to 4 (%)	Grade 3 to 4	Grade 3 to 4 (%)
Total Pts	78	29.1	16	15.7
Malignant Neoplasm	11	4.10	2.0	2.0
Metastatic Malignant melanoma	4	1.5	0	0
Abdominal pain	5	1.9	0	0
Back Pain	4	1.5	1	1
Atrial fibrillation	3	1.1	0	0
Cardiac arrest*	3	1.1	0	0
General physical health deterioration	4	1.5	0	0
Dyspnea	1	0.4	2.0	2.0
Pneumonia	2	0.7	0	0
Sepsis	3	1.1	0	0
Urinary tract infection	3	1.1	0	0
Dehydration	3	1.1	0	0
Hypotension	3	1.1	1	1
* Cardiac arrest includes cardio-respiratory arrest; These data are from Table 8 in the Clinical Safety Review				

3.1.4 Common Adverse Events:

In study CA-037, the majority of patients in both treatment arms experienced at least one (1) AE [95.1% nivolumab and 93.1%, inv. choice]. In the nivolumab group, the most frequently reported AEs in $\geq 10\%$ of patients were: fatigue 39%, 2 events Grade 3 or 4;

nausea 24%, 1 event Grade 3 or 4; diarrhea 24%, 1 event Grade 3 or 4; vomiting 20%, 1 event Grade 3 or 4; pruritus 19%, 0 Grade 3 or 4; anemia 16%, 5 Grade 3 or 4; cough 15%, 0 Grade 3 or 4; and dyspnea 15%, 1 event Grade 3 or 4. See the **Appendix**, to this review, **Table 5** with details on the most common AEs ($\geq 10\%$) with nivolumab treatment compared to the inv. choice treatment.

3.2 ADVERSE EVENTS OF SPECIAL INTEREST AND IMPORTANCE

The immune-mediated (IM) AEs reported with exposure to nivolumab involve major system organ system classes and are serious, potentially life-threatening and fatal. These data below are extracted from analyses through 30 days after the last dose of nivolumab (b) (4) (based on *internal DOP-2 discussion* on November 26, 2014).

Immune-Mediated Pneumonitis or Interstitial Lung Disease

Due to the known risk of pneumonitis with exposure to nivolumab, hypoxia and dyspnea were included in the preferred term (PT) analysis for the clinical event of pneumonitis. It is important to note that the protocol for study CA-307 included routine measurement of oxygen saturation by pulse oximetry every 2 weeks during treatment with nivolumab. As explained by the Clinical Safety Reviewer, the PT pneumonia was not included in the analysis due to the high frequency with which pneumonia was expected to be reported in this study population and in consideration of infectious etiologies rather than non-infectious pneumonitis.

Severe pneumonitis or interstitial lung disease, including fatal cases, was experienced with nivolumab exposure. Per the Clinical Safety Reviewer, across the clinical trial experience of 1,524 patients, the incidence of fatal IM pneumonitis was less than 0.5%. In study CA-307, pneumonitis or interstitial lung disease was reported in 3.4% of 268 patients exposed to nivolumab and none of the 102 patients exposed to the inv. choice of chemotherapy. One (1) Grade 3 and 5 Grade 2 cases of pneumonitis were experienced in the nivolumab treated patients. The median time to onset for all cases was 9.1 weeks (range 3.6 to 26 weeks).

The clinical status of 5 of 9 patients required high-dose corticosteroids (≥ 40 mg prednisone or equivalents per day) for a median duration of corticosteroid treatment of 4.1 weeks (range of 2.3 to 5 weeks). Per the Clinical Safety Reviewer, pneumonitis resolved in the 5 patients with a median time-to-resolution with a median time-to-resolution of 6 weeks. Resolution of the remaining four patients was not documented. See the Clinical Safety Review (b) (4)

(b) (4) for additional details.

Immune-Mediated Colitis and/or Diarrhea

Gastrointestinal (GI) events for the risk of IM colitis and/or severe diarrhea were analyzed with the PTs of colitis, colitis ulcerative, diarrhea, enteritis, enterocolitis, frequent bowel movements and GI perforation. The Clinical Safety Reviewer extended the reporting time to be 100 days after the last dose of treatment to better characterize the risks of IM colitis and/or severe diarrhea. Adverse events reported as GI AEs were reported in 57 (21.3%) of patients in the nivolumab group and 18 (17.6%) patients in the

inv. choice group. The most frequently reported term ($\geq 10\%$), regardless of causality, was diarrhea in both the nivolumab and the inv. choice groups.

Five (2%) patients treated with nivolumab experienced Grade 3 colitis and required permanent discontinuation of nivolumab compared to no patients treated with the inv. choice of chemotherapy. The median time to onset for colitis was reported as 8.3 weeks (range 0.1 weeks to 37.6 weeks). Each of these 5 patients required high-dose corticosteroid treatment. One patient (0.4%) with Grade 3 colitis required permanent discontinuation of nivolumab. Resolution of the colitis was not documented for the remaining four patients with Grade 3 colitis. The substantially complete nivolumab labeling includes recommendation to monitor patients for IM colitis and withhold or discontinue nivolumab for IM colitis of Grade 2 or higher severity.

The substantially complete nivolumab labeling includes the recommendation to initiate high-dose corticosteroids for severe (Grade 3) diarrhea or colitis. For moderate (Grade 2) diarrhea or colitis, labeling recommends to withhold nivolumab, and if the diarrhea and/or colitis persist, to manage with corticosteroids. If there is worsening or no improvement despite initiation of corticosteroid, per proposed labeling, permanently discontinue nivolumab.

Immune-Mediated Hepatotoxicity

In study CA-307, among a total of 268 patients, hepatotoxicity, with elevations in transaminases [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)] was reported in 31 (12%) treated with nivolumab and 8 (7.8%) patients treated with the inv. choice. Grade 3 to 4 increases in transaminases occurred in 10 (4%) of nivolumab-treated patients and in two (2) patients (2%) of patients treated with the inv. choice. The median time to onset was 4.1 weeks in both treatment-groups, nivolumab and the inv. choice (b) (4)

High-dose corticosteroids were employed for 10 patients treated with nivolumab for a median duration of 13 weeks. One patient (0.4%) with Grade 3 ALT elevation required permanent discontinuation of nivolumab. The nivolumab dose was delayed in four patients. The Clinical Safety Reviewer reports resolution of the reported hepatotoxicity in 3 (10%) of 31 patients. There are no cases of Hy's Law reported among these data.

See the Clinical Safety Review (b) (4)

(b) (4) for additional details on hepatotoxicity with exposure to nivolumab.

Immune-Mediated Endocrine Disorders

Endocrine disorders (specifically, adrenal disorders, pituitary disorders, and thyroid disorders) were analyzed through 30 days after the last dose of nivolumab. Thyroid function tests were evaluated at baseline and throughout study CA-307. Severe thyroid disorders were observed with exposure to nivolumab.

The incidence of hypothyroidism, including autoimmune thyroiditis, was 7.8% (21) of 268 patients treated with nivolumab and zero (0) patients in the inv. choice chemotherapy group. The median time to onset of the hypothyroidism was 10.7 weeks from first exposure to nivolumab.

Hyperthyroidism was reported in 3% (8 of 268 patients) treated with nivolumab and 1% (1 of 102 patients) treated with the inv. choice. The median time of onset of hyperthyroidism was 7.1 weeks with nivolumab treatment. The majority (6) of these 8 patients experienced resolution of the hyperthyroidism.

Proposed labeling includes the recommendation to monitor thyroid function prior to initiation of nivolumab therapy and, periodically, during nivolumab treatment. Replacement thyroid therapy is indicated for isolated hypothyroidism. (b) (4)

Adrenal insufficiency was reported in 1.1% (3 of 268 patients) treated with nivolumab and one of these cases was assessed as Grade 3 adrenal insufficiency. Nivolumab treatment was withheld in all three patients; corticosteroids were employed to stabilize these cases of adrenal insufficiency.

Immune-Mediated Renal Failure and Nephritis

Study CA-307 included routine testing for creatinine and blood urea nitrogen (BUN) every 2 weeks during nivolumab therapy. Renal AEs were reported in 18 (6.7%) of patients treated with nivolumab and 4 patients (3.9%) of patients treated with the inv. choice of chemotherapy. The most frequently reported AE was blood creatinine increased in the nivolumab group and acute renal failure in the inv. choice group.

In study CA-307, nephrotoxicity was reported in 4 (1%) of 268 patients treated with nivolumab. Grade 3 tubulointerstitial nephritis was reported in 1 (0.4%) of nivolumab treated patients. Two of these 4 patients, including the one patient with Grade 3 tubulointerstitial nephritis, were treated with high-dose corticosteroids for a median duration of 1.9 weeks. All 4 patients experienced resolution of nephrotoxicity.

Proposed labeling includes recommendation that for severe (Grade 3) or moderate (Grade 2) serum creatinine elevation, that nivolumab be withheld and corticosteroids are initiated. For life-threatening (Grade 4) serum creatinine elevation, permanently discontinue nivolumab and initiate high-dose corticosteroids.

Immune-Mediated Pancreatitis

Two (2) patients (0.7%) experienced acute pancreatitis out a total of 268 patients treated with nivolumab and zero patients treated with the inv. choice. These two patients experienced Grade 3 pancreatitis, required hospitalization, were treated with high-dose corticosteroids, and had nivolumab treatment discontinued. Pancreatitis is cited in proposed labeling (*Section 5.7 Warnings and Precautions, and Section 6. Adverse Reactions*). See the Clinical Safety Review with additional details on withholding nivolumab treatment in the presence of acute pancreatitis.

Immune-Mediated Skin Reactions

Exfoliative dermatitis, erythema multiforme, vitiligo, and psoriasis were reported as IM-AEs with nivolumab exposure. See the Clinical Safety Review for additional details on skin AEs as well as other events with causality attributed to nivolumab.

3.3 90-DAY SAFETY UPDATE REPORT

The 90-day safety update report (SUR) on nivolumab was submitted on October 28, 2014. The AEs reported were consistent with the clinical safety data reported above. There were no new AEs reported in the 90-Day SUR. See the Clinical Safety Review for details on the 90-Day SUR.

4 DISCUSSION

Nivolumab, a NME, is a programmed death receptor-1 inhibitor that demonstrated durable anti-tumor activity at 3 mg/kg Q2W in refractory patients with unresectable or metastatic melanoma in the pivotal study CA-037 by an ORR of 31.7% (95% CI: 23.5, 40.8) based on analysis of the first 120 nivolumab-treated patients with at least 6 months of follow-up. The median DOR among the responders demonstrated a range of 1.4+ months to 10.0+ months, supporting the potential for nivolumab to induce longer term durable responses compared to available chemotherapy, the investigators choice of chemotherapy. The median DOR for the investigator's choice demonstrated 3.6 months with a range of 1.3+, 3.5 months.

The most important serious risks associated with use of nivolumab are immune-mediated (IM) based on the mechanism of action of this programmed death receptor-1 inhibitor. Among all reported IM AEs associated with use of nivolumab, the most serious IM-AEs, and some life-threatening and fatal, are pneumonitis; colitis and severe diarrhea; hepatotoxicity; endocrine disorders including thyroid dysfunction, adrenal insufficiency and hypophysitis; renal failure and/or nephritis; and pancreatitis. Each of these serious IM AEs was reported to be higher in the nivolumab treatment group than in the investigator's choice. See **Section 3.1 Clinical Safety**, in this review for details of these clinical safety data including fatalities with causality.

The serious IM-AEs associated with use of nivolumab are similar but less severe than the IM-SAEs reported with ipilimumab as well as those reported with pembrolizumab. Ipilimumab was approved in 2011 with a Boxed Warning and a REMS. Pembrolizumab, approved in September 2014, was not required to have a Boxed Warning or a REMS. A Boxed Warning was seriously considered for nivolumab based on the severe, life-threatening, and potentially fatal pneumonitis; however, the majority of fatalities secondary to pneumonitis were not in patients in this clinical development program for malignant melanoma (rather, the majority of fatalities secondary to pneumonitis were in patients in with non-small cell lung cancer). The concern about fatal pneumonitis does not appear to be as great a risk in the malignant melanoma patient population compared to NSCLC population. The DOP-2 concluded not to require a Boxed Warning for fatal pneumonitis in labeling for nivolumab proposed for the treatment of malignant melanoma.

The applicant submitted a RMP with proposed non-REMS materials based on a failure modes and effects analysis (FEMA) to proactively identify as a systematic approach to proactively identify when and how a system may fail, assess the relative effects of such failures, and ways to prevent the failures based on the serious risks reported with nivolumab. Based on the outcome of the FEMA, the applicant proposed materials to inform oncology providers on appropriate patient screening and monitoring during treatment with nivolumab. The applicant proposed non-REMS materials for oncology providers to counsel oncology patients emphasizing the need for vigilance and prompt

reporting of specific symptoms and signs with nivolumab treatment. The proposed materials include:

(b) (4)

a patient wallet card and a Medication Guide (part of proposed labeling).

The DHP and the DRISK agree that oncology providers need to understand the severe, life-threatening, and potentially fatal risks associated with use of nivolumab. However, the DHP and the DRISK concurred that these risks can be communicated through labeling and a REMS is not required to ensure that the benefits of nivolumab outweigh the risks. If approved, the likely target prescribers for nivolumab will be oncologists and likely the same oncology providers who prescribe ipilimumab and pembrolizumab. Based on the healthcare provider surveys for the Yervoy REMS, oncology providers are informed and understand the IM-AEs associated based on use of IPI (approved March 2011) for the treatment of unresectable or metastatic melanoma and are familiar with the clinical management of IM-AEs in this high risk patient population.

The DOP-2 concluded that the proposed non-REMS materials should be available to oncology providers and oncology patients to inform on the severe, life-threatening, and potentially fatal IM- severe AEs associated with use of nivolumab, if it should be approved. The DRISK does not disagree with the applicant providing non-REMS materials to be made available to oncology providers and oncology patients. However, the DRISK concludes that the proposed non-REMS are not necessary to ensure that the benefits of nivolumab outweigh the risks associated with its use. Note that these non-REMS materials are considered promotional and will be reviewed by the OPDP.

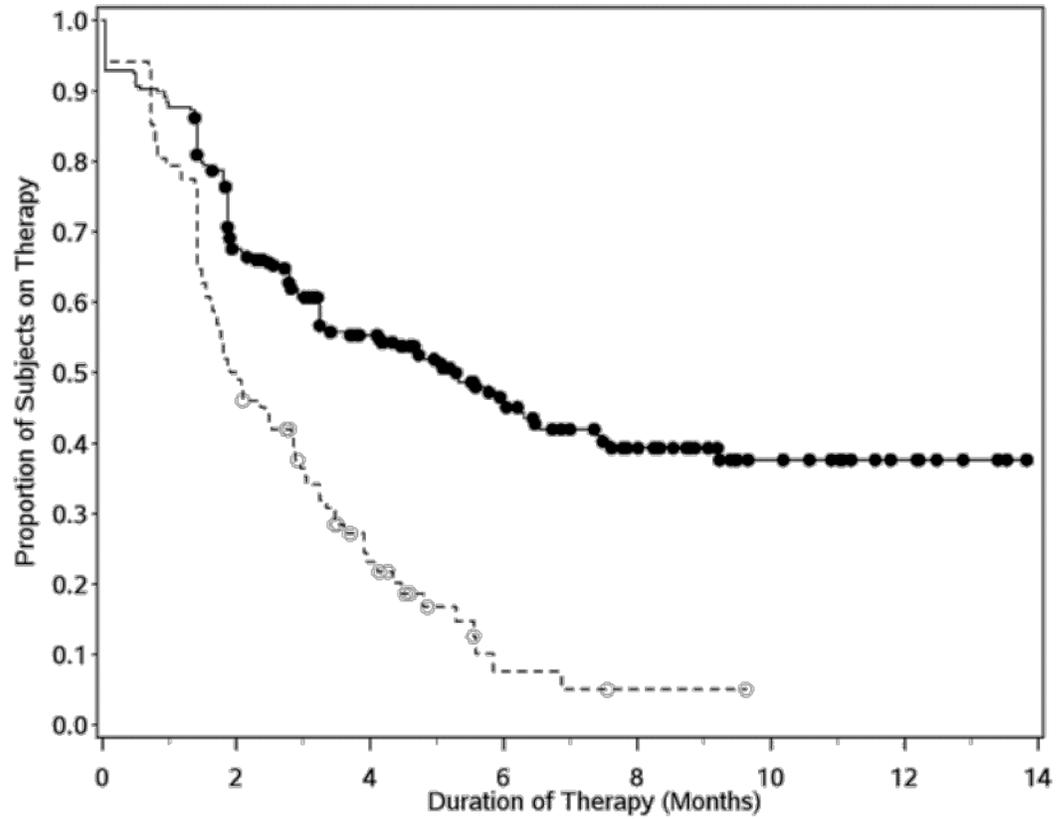
The DOP-2 has not yet communicated to the applicant the proposed postmarketing commitments (PMCs) and one postmarketing requirement (PMRs) for BLA 125-554 Opidivo (nivolumab). Because nivolumab is being reviewed under Subpart E, Accelerated Approval, a confirmatory clinical trial will be required as a PMR to verify and describe the clinical benefit of nivolumab in the proposed population, i.e., patients with unresectable or metastatic melanoma. These patients have a serious and life-threatening condition with an unmet medical need.

5 CONCLUSION

The DRISK and the DOP-2 concur that, at this time, a REMS is not necessary to ensure that the benefits of nivolumab outweigh the reported risks of the proposed nivolumab injection, as an intravenous infusion, for the treatment of unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The DOP-2 should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for nivolumab injection.

APPENDIX: See the next page.

Figure 1.2.2-1: Kaplan-Meier Plot of Duration of Study Therapy - All Treated Subjects



Number of Subjects at Risk

NIVOLUMAB

268 174 111 63 38 16 8 0

INVESTIGATOR'S CHOICE

102 51 17 3 1 0 0 0

—●— NIVOLUMAB (events : 139/268), median and 95% CI : 5.26 (3.29, 6.47)

--○-- INVESTIGATOR'S CHOICE (events : 84/102), median and 95% CI : 1.95 (1.61, 2.86)

Table 5. Most Common Adverse Events ($\geq 10\%$ in the Nivolumab Treatment Group)

Adverse Event	Nivolumab N = 268		Inv. Choice N = 102	
	Total %	Grade 3 or 4 %	Total %	Grade 3 or 4
Any Event	95	34	93	43
Fatigue	39	2	43	5
Nausea	24	1	42	2
Diarrhea	24	1	42	2
Vomiting	20	1	17	2
Pruritus	19	0	4	0
Anemia	16	5	28	8
Cough	15	0	5	0
Dyspnea	15	1	15	2
Decreased appetite	15	0	18	0
Pyrexia	13	0	10	1
Constipation	13	1	20	1
Arthralgia	13	0	15	2
Rash	12	0	5	0
Abdominal pain	11	3	7	0
Headache	11	1	11	0
Peripheral edema	10	0	5	0
These data are per the Clinical Safety Reviewer.				

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/s/

CAROLYN L YANCEY

12/04/2014

REMS Review for OPDIVO (nivolumab) dated December 4, 2014.

CYNTHIA L LACIVITA

12/05/2014

Concur