CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125554Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy
Application Number(s)	BLA 125554
Priority or Standard	Priority
Submit Date(s)	July 30, 2014
Received Date(s)	July 30, 2014
PDUFA Goal Date	March 30, 2015
Division / Office	DOP2 / OHOP
Reviewer Name(s)	Maitreyee Hazarika (safety) Meredith Chuk (efficacy) Marc Theoret (TL)
Review Completion Date	December 5, 2014
Established Name	Nivolumab / BMS-936558
(Proposed) Trade Name	Opdivo
Therapeutic Class	Monoclonal antibody
Applicant	Bristol Myers Squibb
Formulation(s)	Solution
Dosing Regimen	3 mg/kg IV every 2 weeks
Indication(s)	Treatment of patients with unresectable or metastatic melanoma who progressed after treatment with anti-CTLA4 therapy, and if BRAF V600 mutation positive, a

	BRAF inhibitor
Intended Population(s)	≥ 18 years of age

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewers recommend accelerated approval [(Subpart E (21CFR601.41)], of nivolumab for the treatment of adult patients with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab, and, if BRAF V600 mutation positive, a BRAF inhibitor, at a dose of 3 mg/kg intravenously every 2 weeks.

The clinical data presented in the BLA demonstrate the efficacy of nivolumab in confirmed overall response rate 31.7% (95% CI: 23.5, 40.8) by blinded independent central review (BICR) which appears to be durable (range 1.4 to 10+ months). The median duration of response was not reached with 87% of patients who obtained a response maintaining that response at the time of data cut-off.

The safety profile of nivolumab is consistent with an immunologically mediated anti-cancer therapy and is acceptable, given the serious and life-threatening nature of advanced, refractory melanoma.

1.2 Risk Benefit Assessment

Patients with advanced melanoma who have progressed following therapy with ipilimumab, and a BRAF inhibitor if indicated, represent a patient population with an extremely poor prognosis, for which there is an unmet medical need. FDA-approved therapies for patients with unresectable or metastatic melanoma which may be used in this population include dacarbazine and interleukin-2 (IL-2) and are expected to be of limited effectiveness based on low overall response rates observed with both products and, with IL-2, the potential for substantial toxicity in a treatment refractory setting.

The clinical benefit of nivolumab is primarily based upon the results from Trial CA209037, a randomized (2:1), multi-center, open-label, trial of nivolumab vs. investigator's choice chemotherapy in patients with 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 a BRAF inhibitor. In the interim single-arm efficacy analysis of blinded independent central review (BICR)-assessed, confirmed objective response rate (ORR) per RECIST v1.1 in 120 patients treated with nivolumab at a dose of 3mg/kg every 2 weeks with at least 6 months of follow-up, the ORR was 31.7% (95% CI: 23.5, 40.8). Thirty-eight patients had an objective response; four patients (3.3%) had a complete response (CR) and 34 patients (28.3%) had a partial response (PR). The median duration of response (DOR) was not reached (range 1.4 to 10+ months); however 87% of the responses were ongoing at the

time of data cutoff, with 13/38 patients with ongoing responses of 6 months or longer. Most patients responded by the first disease assessment at 9 weeks; four of the 38 patients achieved a response after 16 weeks of nivolumab. The treatment effect of nivolumab was observed in patients who were PD-L1 positive [43.6% (95% CI: 30.3, 57.7)] as well as patients who were PD-L1 negative or indeterminate [20.3% (95% CI: 11.3, 33.6)]. The true impact of tumor PD-L1 expression in this preliminary analysis is unclear as the statistical design of the trial was not adequate to answer this question and the assay used per BMS was a verified, though not validated assay. A premarketing application (PMA) has not been submitted for use of the BMS assay as a companion diagnostic for selection of melanoma patients prior to treatment with nivolumab. The treatment effect of nivolumab appeared consistent across subgroups based on demographics and baseline disease characteristics.

The clinical benefit of nivolumab is supported by the results in the dose finding Trial CA209003 in which 87 patients received doses at or below 3mg/kg every 2 weeks. The ORR in these 87 patients was 34.5% (95% CI: 24.6, 45.4), the median DOR was 22.9 months (95% CI: 16.6, NR) with a range of 3.9+ to 26.5 months. Patients in this study were naïve to ipilimumab but of the 107 patients with refractory melanoma, all but one was previously treated with chemotherapy and 61.6% received two or more prior regimens, representing a heavily pre-treated patient population. The similar ORR and longer duration of follow up with median sustained responses of 23 months in this study provides additional supportive evidence of effectiveness of nivolumab in patients with refractory melanoma.

The primary safety risks of nivolumab are immune-mediated adverse events which occurred in 59% of patients in the nivolumab group. The most common immune-mediated adverse events in more than 2% of patients were rash, diarrhea, pruritus, hepatotoxicity, hypothyroidism, vitiligo, pneumonitis, hyperthyroidism, and dermatitis. Seven percent of all immune-mediated events were Grade 3 or 4. Also observed at a lower frequency were colitis, nephritis, autoimmune thyroiditis, adrenal insufficiency, uveitis, autoimmune neuropathy, demyelination, pancreatitis, and facial and abducens nerve paresis. Identification of additional immune-related adverse reactions is expected through routine pharmacovigilance as detection of low-frequency adverse events is limited in a relatively small safety database. One patient required additional immune-modulating agents for the treatment of pancreatitis. Immune-related adverse reactions appear manageable with corticosteroids.

The most common adverse events (AEs) (≥ 20%) observed with nivolumab 3 mg/kg administered intravenously every 2 weeks were fatigue, musculoskeletal pain, nausea, rash, and diarrhea. Nine percent of patients required treatment discontinuation and 25.7% required dose delays. The most frequent AEs (≥1%) leading to dose delays of nivolumab were dyspnea (2.6%), elevated lipase, increased amylase, and pneumonitis (1.5% each), and abdominal pain, adrenal insufficiency, arthralgia, and headache (1.1% each).The most frequent (≥2%) Grade 3-4 AEs were malignant neoplasm progression

(7.8%), anemia (4.9%), abdominal pain (3.4%), hyponatremia (2.6%), and elevated aspartate aminotransferase, elevated lipase, vomiting, and general physical health deterioration (2.2% each). Approximately half (50.4%) of patients experienced serious adverse events (SAEs). The most common SAEs occurring in ≥ 2% of patients included malignant neoplasm progression (20.9%), metastatic malignant melanoma (2.6%), and back pain (2.2%).

The risk benefit assessment is favorable for the use of nivolumab for the treatment of adult patients with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab, and, if BRAF V600 mutation positive, a BRAF inhibitor, at a dose of 3 mg/kg intravenously every 2 weeks. Unresectable or metastatic melanoma that is refractory to ipilimumab and a BRAF inhibitor is a serious and life-threatening disease. Pembrolizumab received accelerated approval in September 2014 for this refractory patient population. Nivolumab has shown evidence of anti-tumor activity with a clinically significant confirmed overall response rate, evidence of durability of the responses, and an acceptable toxicity profile, given the serious and life-threatening nature of advanced, refractory melanoma.

The reviewers do not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of nivolumab and the experience of the medical community in managing immune-mediated adverse reactions from other FDA-approved immune-modulating agents, ipilimumab and pembrolizumab. Risk management based on labeling, including a non-REMS patient medication guide, will be employed to ensure the safe and effective use of nivolumab.

Recommendation for Accelerated Approval versus Regular Approval

Subpart E (21CFR601.41), describes accelerated approval of biologic products for serious and life-threatening illnesses based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity that provides meaningful therapeutic benefit to patients over existing therapies. Accelerated approval is “subject to the requirement that the applicant study the biologic product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.” The recommendation for accelerated approval for nivolumab rather than regular approval for treatment of patients with unresectable or metastatic melanoma who are refractory to ipilimumab, and if BRAF V600 mutation positive, a BRAF inhibitor, is based upon the following considerations:

- There is uncertainty as to the relation of overall response rate (ORR) and duration of response (DOR) to ultimate outcomes of clinical benefit, including overall survival (OS).
- The median DOR is based upon a small number of patients with limited follow-up duration.

- The ORR of 31.7% with a median duration of response that was not reached but duration that ranged from 1.4+ to 10+ months in a refractory population in this interim analysis is used as a surrogate endpoint that is reasonably likely to predict clinical benefit and appears to provide meaningful advantage over available therapy. Responses were ongoing in 87% of the patients in the nivolumab group at the time of data cutoff and suggest the potential for a durable response in this refractory population with limited available treatment options.
- The early submission of nivolumab in this BLA submission is based on efficacy and safety data from Trial CA209037, which has co-primary endpoints of objective response rate (ORR) and overall survival (OS). Confirmatory evidence of clinical benefit will be based on the final OS analysis, which by demonstrating a clinically meaningful improvement in OS, may be sufficient to convert the application from accelerated to regular approval.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigation Strategies (REMS). It appears that the AEs are reversible with the use of corticosteroids and other immune suppressants. Oncologists have become familiar with the management of immune-mediated adverse events caused by immune-modulators, such as ipilimumab, which is given as an infusion and was approved in 2011. Since early recognition and initiation of treatment, and patient and physician education are keys to limiting the morbidity of immune mediated adverse events, a medication guide for nivolumab describing the risks of immune-related side effects for patient education for safe and effective use will be required.

1.4 Recommendations for Postmarket Requirements and Commitments

Nivolumab is being approved under subpart E (accelerated approval); therefore, confirmatory trial(s) are required to verify and describe the clinical benefit of nivolumab in the proposed population, i.e., patients with unresectable or metastatic melanoma.

PMR1: 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.

2 Introduction and Regulatory Background

2.1 Product Information

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2.

2.2 Tables of Currently Available Treatments for Proposed Indications

Pembrolizumab received accelerated approval for the proposed indication, i.e., patients who progressed following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor; however, pembrolizumab does not constitute available therapy based on the accelerated approval. FDA-approved therapies for patients with unresectable or metastatic melanoma which may be used in this population include dacarbazine and interleukin-2 (IL-2). **Table 1** lists the FDA-approved therapies for metastatic melanoma and the clinical basis for approval.

Table 1: Table of FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma

FDA Approved Drug[1]	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
DTIC (dacarbazine)[2]	1975	Single-arm	ORR	ORR of 5-20%
Proleukin (interleukin-2)[2]	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)[2]	2011	Multicenter, randomized, blinded, active-controlled three-arm	OS ORR	**Ipilimumab vs. gp100**: 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 **Ipilimumab+gp100 vs. gp100**: 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[3] (vemurafenib)	2011	Randomized, open-label active-controlled, two-arm	OS PFS ORR	**Vemurafenib vs. DTIC** 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)

FDA Approved Drug[1]	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
				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[3] (dabrafenib)	2013	Randomized, open-label active-controlled, two-arm	PFS ORR	**Dabrafenib vs. Dacarbazine** 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%
Mekinist[4] (trametinib)	2013	Randomized, open-label active-controlled, two arm	PFS ORR	**Trametinib vs. Chemotherapy** 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[4] (dabrafenib and trametinib)	2014[5]	Randomized, open-label, active-controlled, two arm portion of dose-escalation study	ORR	**Dabrafenib plus Trametinib vs. single-agent Dabrafenib** 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)	2014[6]	Randomized dose-comparison, open-label, uncontrolled two arm cohort	ORR	ORR: 24% (95% CI: 15.2, 33.8) mDOR: NR (range 1.4+, 8.5+m)

Source: Proleukin USPI; Yervoy USPI; Zelboraf USPI; Dacarbazine USPI; Tafinlar USPI; Mekinist USPI; Keytruda 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; 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.
[1] Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.
[2] BRAF V600 mutation status unknown.
[3] Patient selections based on BRAF V600E mutation-positive tumors.
[4] Patient selections based on BRAF V600E or V600K mutation-positive tumors
[5] Accelerated approval as per 21 CFR 314.510 of subpart H
[6] Accelerated approval as per 21 CFR 601, subpart E

2.3 Availability of Proposed Active Ingredient in the United States

Nivolumab is not available in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

The ipilimumab prescribing information includes a boxed warning based on the risk of severe and fatal immune-mediated reactions due to T-cell activation and proliferation. The most common severe immune-mediated reactions included enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. Ipilimumab was approved with a risk evaluation and mitigation strategy. The most common adverse reactions (≥5%) fatigue, diarrhea, pruritus, rash, and colitis. At doses ranging from 0.3 to 10 mg/kg, the following adverse reactions were reported (incidence less than 1% unless otherwise noted): urticarial (2%), large intestinal ulcer, esophagitis, acute respiratory distress syndrome, renal failure, and infusion reaction (Yervoy USPI).

The primary safety risks of pembrolizumab are immune-mediated adverse events which were managed with corticosteroids. The most common immune-mediated adverse reactions included pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. Adverse reactions, reported in at least two patients that led to discontinuation: pneumonitis, renal failure, and pain. The most frequent serious adverse drug reactions reported in 2% or more of patients were renal failure, dyspnea, pneumonia, and cellulitis. The most common adverse reactions (≥20% of patients) included fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. The following clinically significant, immune-mediated adverse reactions occurred in less than 1% of patients treated with: exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma, and adrenal insufficiency, myasthenic syndrome, optic neuritis, and rhabdomyolysis (Keytruda USPI).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for nivolumab.

On June 28, 2006, the initial protocol was submitted to IND100052.

On June 13, 2012, IND115195 was split from IND100052 for the indication of melanoma.

On June 25, 2012, the pre-original Investigational Device Exemption (IDE) packet (pre-IDE L120549) for PD-L1 IHC pharmaDxTM Kit was submitted to Center for Devices and Radiological Health (CDRH).

On July 17, 2012, an End of Phase 1 (EOP1)/pre-Phase 3 meeting was held with the Applicant to provide feedback on the preliminary data from the ongoing Phase 1 study (CA209003) for advanced, unresectable, or metastatic melanoma, and discuss the potential for accelerated approval based on study CA209003. Study CA209037 was planned as an open-label, multicenter, randomized (2:1), active-controlled study to compare BMS-936558 to chemotherapy in approximately 354 patients with Stage III (unresectable) or Stage IV, recurrent or metastatic melanoma. Patients randomized to Arm A (N=236) will receive BMS-936558 3mg/kg dose intravenously on an every 2 week schedule. Patients randomized to Arm B (N=118) will receive dacarbazine or carboplatin/paclitaxel as determined by the investigator. Randomization stratification factors are PD-L1 status, BRAF status, and prior ipilimumab response. The Applicant proposed co-primary endpoints of Objective Response Rate (ORR) and Overall Survival (OS).

- FDA agreed with dacarbazine or paclitaxel and carboplatin as acceptable comparators for the proposed patient population, based on currently available therapies for patients with unresectable or metastatic melanoma after disease progression on ipilimumab and/or BRAF inhibitors (BRAFV600E mutation-positive patients only)
- FDA agreed that a trial design using co-primary endpoints of ORR and OS would be acceptable to support accelerated approval of BMS-936558 based upon a final analysis of ORR that demonstrates an effect that is reasonably likely to predict clinical benefit and confirmatory evidence of clinical benefit based on the final OS analysis, which demonstrates a clinically meaningful improvement in OS, would be sufficient to convert the application from accelerated to regular approval or to support regular approval
- FDA agreed that study CA209037 have adequate power to detect treatment effects of BMS-936558 in PD-L1 biomarker negative and positive subgroups; type I error allocation based on hypothesis testing in multiple subgroups; completion of analytical validation studies of the PD-L1 in vitro diagnostic test kit prior to initiating the trial; alternate trial designs, including adaptive designs, to demonstrate the prognostic and/or predictive effect of the PD-L1 biomarker
- FDA agreed that overall survival is sufficient to make a risk-benefit determination for full approval

On August 31, 2012, a Pre-IDE teleconference was held with CDRH (including CDER representation) to discuss the PD-L1 IHC as a companion diagnostic being developed in collaboration with Dako.

On October 4, 2012, the Applicant was granted Fast Track Designation for treatment of patients with unresectable or metastatic melanoma to demonstrate a clinically important and statistically robust improvement in overall survival over available therapies.

On October 17, 2012, Protocol CA209037, A Randomized, Open-Label Phase 3 Trial of BMS-936558 Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy, was submitted to the IND.

On October 29, 2012, the IDE was converted to pre-submission for Pre-Market Application (PMA) per request from CDRH.

On January 23, 2013, Orphan Drug Designation was granted for the treatment of stage IIb to IV melanoma.

On January 23, 2013, Breakthrough Therapy Designation was denied based on the following: (1) limited data regarding the details of the prior therapy administered for unresectable or metastatic melanoma, (2) no information was provided regarding the BRAF mutation status, (3) and response rates with nivolumab 31.1% (95% CI: 22.5%, 40.9%) not substantially superior to the response rates observed with available BRAF inhibitor therapy and not of sufficient magnitude to be likely to predict an effect on overall survival that is substantially superior to the survival effect with ipilimumab.

On March 5, 2013, the PMA pre-submission supplement was submitted.

On March 27, 2013, an Advice/Information letter on the protocol CA209037 and CA209017:

- FDA recommended that an independent review committee-determined ORR be considered the primary efficacy endpoint to support a regulatory action; investigator-determined ORR may be included as a secondary endpoint with sufficient allocation of Type I error and adjustment for multiplicity; and ORR have to be confirmed.

On June 5, 2013, exemption was granted from submitting pediatric study plan for pediatric development in melanoma due to orphan designation.

On September 12, 2013, the PMA Modular Submission Shell was submitted to CDRH.

On October 3, 2013, a Type C Meeting was held with the Applicant to discuss their updated nivolumab global registration strategy, and potential initiation of an expanded access program (EAP), for nivolumab as monotherapy in non-small cell lung cancer

(NSCLC), melanoma, and renal cell carcinoma (RCC) and in combination with ipilimumab for melanoma. The Applicant proposed "decoupling" the ORR from the interim analysis of OS in study CA209037 to accelerate the development.

- FDA agreed to review a proposal for an alternate timing of the final ORR analysis in protocol CA 209037

On October 25, 2013, the Applicant submitted a proposal for an alternate timing of the final ORR analysis in protocol CA209037 to accelerate the development of nivolumab in subjects with advanced unresectable or metastatic melanoma in protocol CA209037.

On January 6, 2014, the Applicant submitted the revised protocol CA209037 (No. 3) that planned for a formal ORR analysis that was no longer linked to the interim overall survival (OS) analysis. The formal analyses of ORR and OS will be conducted at different timepoints ("decoupled") with ORR being analyzed first followed by interim and final OS analyses. On January 16, 2014, FDA sent an Advice/Information letter with the following recommendation:

- FDA did not agree with the proposed change in alpha allocation to the co-primary endpoints and recommended to modify the statistical plan

On February 12, 2014, the Applicant submitted the modification to primary analysis of ORR in CA209037 to incorporate an analysis of independent review committee-assessed ORR in the first 120 patients treated with nivolumab in order to seek accelerated approval. OS remains a co-primary endpoint and will serve as confirmation of clinical benefit (full approval). On March 17, 2014, FDA sent an Advice/Information letter with the following:

- FDA agreed to the plan to analyze confirmed ORR based on independent review in 120 nivolumab-treated patients, with the goal of excluding an ORR of less than 15% (based on the lower 99% confidence interval).
- FDA agreed with the proposed plan of using an alpha of 0.04 for the analysis of OS is acceptable. However, the FDA recommendation was to consider allocating 0.001 alpha for the ORR analysis and allocating 0.049 alpha for the OS analysis.

On April 9, 2014, the Applicant submitted Protocol CA209168, Expanded Access Program with Nivolumab for Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma Progressing Post Prior Systemic Treatment Containing an Anti-CTLA-4 Monoclonal Antibody.

On May 19, 2014, a Type C meeting was held to discuss the planned PD-L1 analysis plan for the nivolumab registration studies in the indications of NSCLC, RCC, and melanoma.

- FDA recommended to request a meeting with each indication review team separately to obtain the best guidance for the statistical analysis biomarker plan related to their indication

- FDA agreed the PD-L1 analysis plan would be exploratory, and recommended a prospective analysis

On May 23, 2014, the Applicant submitted a revised protocol CA209037 (No. 4) that incorporated the co-primary endpoint to allow a non-comparative estimation of ORR on the nivolumab arm and included allocations of .0.001 alpha for the ORR analysis and 0.049 alpha for the OS analysis per the FDA recommendation provided on February 12, 2014.

On July 9, 2014, a Type B, Pre-BLA meeting was held to provide feedback on the submission plan for the planned BLA and the potential for accelerated approval based on ORR in Study CA209037. At the meeting:

- FDA agreed on the integrated summary of safety, integrated summary of efficacy, and risk management strategy
- Applicant agreed to FDA recommendations, including the format and content of the BLA, the SDTM and AdaM package, narratives, case report forms, safety update.

On July 18, 2014, the Applicant submitted a request for Breakthrough Therapy Designation which was granted on September 11, 2014 based on preliminary evidence from Trial CA209037 which indicated that the treatment effect of nivolumab may represent a substantial improvement over existing therapies for the treatment of unresectable or metastatic melanoma progressing after ipilimumab therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to ipilimumab therapy. A 31.7% objective response rate with single-agent nivolumab was observed in patients with a median duration of response not reached (range of 1.4 - 10+ months).

2.6 Other Relevant Background Information

Regulatory Actions in Other Countries

Nivolumab was submitted for marketing authorization in Japan by Ono Pharmaceutical and was approved for treatment of unresectable melanoma on July 4, 2014. The approved dose of nivolumab in Japan is 2 mg/kg administered as an IV infusion Q3W.

The Applicant provided spontaneous postmarketing cases from Japan reported for nivolumab from July 4, 2014 to July 29, 2014 of two individual safety reports which consisted of one malignant neoplasm progression with fatal outcome, and a nonserious event of infusion-related reaction with unknown outcome.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application appear acceptable.

3.2 Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with Good Clinical Practice, as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50). The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol, amendments, and subject informed consent received appropriate approval by the IRB/IEC prior to initiation of study at the site. No breaches of the conditions and principles of Good Clinical Practice (GCP) in connection with the study or protocol were reported.

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) to perform an audit of three clinical study sites and the Contract Research Organization (CRO) to identify any data quality issues and to document that the study was performed according to GCP: Site #50 (David Minor, MD); Site #16 (Jeffrey Weber, MD); Site # 28 (Sandra P. D'angelo, MD); and the CRO (b) (4) The reviewers selected clinical sites for inspection based on enrollment characteristics, patterns of treatment responders, and protocol violations reported for the sites and the CRO which assessed the BICR.

One clinical site inspected, David Minor, MD (Site #50) was issued a Form FDA 483 citing the following observations.

Observation1: an investigation was not conducted in accordance with the signed statement of the investigator and the investigational plan. Specifically, SAEs were not reported to the sponsor within the 24 hour timeframe in the following patients.

- For patient 37150, death occurred on (b) (6) the site was made aware of the SAE on (b) (6), but there was no documentation on site for reporting the SAE to the sponsor. The same patient was hospitalized on (b) (6) and aware of the SAE on (b) (6) but reported to the sponsor on (b) (6)
- For patient 37131, death occurred on (b) (6) the site was made aware of the AE on (b) (6) but there was no documentation on site for reporting the SAE to the sponsor.

- For patient 37189, death occurred on (b) (6) the site was made aware on (b) (6), but reported to the sponsor on (b) (6)
- For patient 37594, death occurred on (b) (6), the site was made aware of the SAE on (b) (6), but there was no documentation on site for reporting the SAE to the sponsor.
- For patient 37006, hospitalization occurred on (b) (6) the site was made aware on (b) (6) but there was no documentation on site for reporting the SAE to the sponsor. For the same patient, the SAE of dehydration which occurred on (b) (6), the site was made aware, but there was no documentation on site for reporting the SAE to the sponsor.
- For patient 37267, study drug was administered on (b) (6) and (b) (6) but there was no documentation on site reporting the deviation from the protocol to the sponsor.
- There was no documentation of sub-investigator training to ensure that they were informed of their obligations for the trial.

Observation 2: failure to report promptly to the Institutional Review Board (IRB) all unanticipated problems involving risk to human subjects or others. Specifically, the SAEs for patients 37150, 37131, 37189, 37594, 37006, and protocol violation for patient 37267 were not reported to the IRB for the trial.

Reviewer Comments:
1. Out of the six patients at Site #50, four (CA209037-50-37006, CA209037-50-37131, CA209037-50-37189, and CA209037-50-37267) were treated with nivolumab, and two patients (CA209037-50-37150 and CA209037-50-37594) were treated with investigator's choice. The patients treated with nivolumab were reviewed in detail. Since the specific SAEs were not mentioned, the reviewer was unable to determine whether all the SAEs were captured in the dataset. SAEs for patient CA209037-50-37006 reported in the dataset included postoperative ileus, dehydration and metastatic malignant melanoma. Dehydration, mentioned above, was reported in the dataset. All three SAEs lead to hospitalizations. On (b) (6) the patient was hospitalized for metastatic malignant melanoma. SAEs for patient CA209037-50-37131 reported in the dataset included malignant neoplasm progression which was a Grade 5 AE. The date on which death occurred for patient CA209037-50-37131 was reported in the dataset as (b) (6) consistent with the date in the report above. Death was due to malignant neoplasm progression. SAEs for patient CA209037-50-37189 reported in the dataset included cardiac arrest and malignant neoplasm progression. The date on which death occurred for patient CA209037-50-37189 was reported in the dataset as (b) (6) consistent with the date in the report above. Death was due to malignant neoplasm progression. The inspectional observations should not importantly impact data generated by the site and should not impact the overall integrity of the data used in the analyses of safety in trial CA209037.
2. No actions were indicated for Sites #16 and 28.

3. The OSI report for the CRO was pending at the time of the completion of this review.

3.3 Financial Disclosures

In accordance with 21 CFR 54.2, the Applicant submitted a list of the CA209037 study investigators attached to FDA form 3454 certifying that the Principal Investigators and Sub-investigators had no financial information to disclose as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the study. Fouad Namouni, MD, Vice President, Development Lead Nivolumab, certified this disclosure for the Applicant.

Financial disclosure information was collected and reported for 671 Investigators, 668 Principal Investigators and Sub-investigators participating in Trial CA209037 and three independent radiology review committee readers from (b) (4) The Applicant states that all but three Investigators have signed Financial Disclosure Forms.

Out of the 668 Principal Investigators and Sub-investigators participating in Trial CA209037, 638 had no financial information to disclose. Disclosable interest information was provided for 27 Principal Investigators and Sub-investigators, all due to receipt of significant payments of other sorts. Financial disclosure information was not available for three Sub-investigators. The Applicant conducted due diligence for the missing disclosures including three written requests and two telephone calls.

The three radiologist reviewers from (b) (4) who conducted the blinded, independent central review of tumor response and progression in Trial CA209037 did not report any disclosable information.

The following Investigators had disclosable financial information in the category of significant payments of other sorts:

- (b) (6) and Sub-investigators (b) (6) at sites (b) (6) receipt of funding from research grants during the conduct of the trial: $250,000 beginning (b) (6); $2,212,500 beginning (b) (6) $132,610 beginning (b) (6); and $416,520 beginning (b) (6)
- (b) (6) Sub-investigator at site (b) (6) receipt of funding from research grants during the conduct of the trial: $136,450, $101,759, $65,000 and $85,000 all beginning (b) (6); $2,889,000 beginning (b) (6); $750,000 beginning (b) (6); and $30,000 and $170,502 both beginning (b) (6)
- (b) (6) Sub-investigator at site (b) (6) receipt of funding from research grants conducted during the trial: $85,000 beginning October 22, 2012; and $150,000 beginning (b) (6)

- [redacted] Principal Investigator, and Sub-investigators [redacted] at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted]; $100,000 beginning [redacted]; and $3,344,500 beginning [redacted].
- [redacted] Investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $56,000 beginning [redacted] with a total of $156,250.
- [redacted] Sub-investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted]
- [redacted] Investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted] and $100,000 beginning [redacted].
- [redacted] Sub-investigator at site [redacted] In [redacted], he finalized a contract with BMS totaling $72,461 [redacted] reported that [redacted] and does not pose any conflict of interest.
- [redacted] Investigator at site [redacted] $51,000 received for participating in the speaker's bureau during 2012-2013.
- [redacted] Investigator at site [redacted] $30,000 received for speaking honoraria
- [redacted] Investigator at site [redacted] $25, 000 received for participating in the speaker's bureau during 2012.

Three Investigators/ Sub-investigators did not provide Financial Disclosure as follows:

- [redacted] Sub-investigator at site [redacted] from [redacted] The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site. [redacted] did sign [redacted] a Financial Disclosure Form for Study CA209067 that reported no disclosable interest.
- [redacted] Sub-investigator at site [redacted] from [redacted] The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining

a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site.

- [redacted] Sub-investigator at site [redacted] from [redacted]. The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site. [redacted] did sign [redacted] a Financial Disclosure Forms for Study CA209025 and CA209067 that reported no disclosable interest.

Reviewer Comment:
The reviewer had a concern with respect to possible bias which arose from the significant payments to the sites. A subgroup analysis for objective response rate (ORR) was conducted whereby efficacy data from the 40 patients treated at sites 0016, 0020, 0023, 0028, 003, 0050, 0052, and 0067 were excluded. The ORR for the nivolumab group in the remaining 90 patients was 29% (95% CI: 19.8, 39.4) and was 8% (95% CI: 1.7, 21.9) for the remaining 37 patients in the investigator's choice group. Excluding these sites did not impact the efficacy evaluation in the treated ORR population.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There were no significant safety or efficacy issues identified related to Chemistry, Manufacturing, and Controls (CMC).

Refer to FDA CMC Review for details.

4.2 Clinical Microbiology

There were no significant safety or efficacy issues related to product quality from a microbiology standpoint.

Refer to the FDA Product Quality Microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

Refer to the FDA Pharmacology/Toxicology Review for details. The following is excerpted from the review.

Nivolumab was evaluated in two repeat dose studies in the cynomolgus monkey and was well-tolerated in the monkey. In both the 4- and the 13-week studies, a diffuse pattern of inflammatory infiltration was observed in organs and tissues, but no target organ toxicity was identified by clinical pathology or histological analysis when nivolumab was administered by weekly or twice-weekly IV injection to cynomolgus monkeys at doses of 1, 10, or 50 mg/kg/week for 13 weeks. In the 13-week study, the thyroid hormones T3 and TSH levels were decreased in high dose females; however, there was no histological correlate and T4 levels were unaffected. Consistent with its mechanism of action, there were increases in CD4+ and CD8+ T cells in the high dose group (50 mg/kg), and a trend toward an increase in CD4+ and CD8+ memory T cells. The pattern of histological binding of nivolumab was assessed in normal cadaveric tissues obtained from both humans and cynomolgus monkeys. A broad pattern of immunoreactivity was observed in lymphocyte populations of many tissues evaluated, particularly circulating blood, breast, gut associated lypmphoid tissue (GALT) of the small intestine, kidney, liver, lung, lymph node, spleen, ovary, pancreas, peripheral nerve, prostate, thymus, tonsil, urinary bladder, and uterus.

4.4 Clinical Pharmacology

Refer to FDA Clinical Pharmacology Review for details.

4.4.1 Mechanism of Action

Nivolumab is a humanized monoclonal antibody of the IgG4/kappa isotype that binds to PD-1 and blocks the interaction between PD-1 and PD-L1 and PD-L2. Both PD-1 and PD-1 ligands are upregulated following initiation of an immune response and help to limit that response to avoid tissue damage. Upregulation of PD-1 ligands also occurs in some tumors and is thought to contribute to inhibition of active T-cell immune surveillance of tumors.

4.4.2 Pharmacodynamics

Not applicable

4.4.3 Pharmacokinetics

Single dose pharmacokinetics (PK) of BMS-936558 (nivolumab) was evaluated in patients with multiple tumor types in MDX1106-01 whereas multiple dose PK was evaluated in patients in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~350 patients from MDX1106-01, MDX1106-02, and CA209003. Single dose PK of nivolumab was evaluated in 39 patients with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear

in the range of 0.3 to 10 mg/kg with dose proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (i.e., CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal half-life of nivolumab is 17 to 25 days. Both the elimination and distribution of BMS-936558 (nivolumab) appear to be independent of dose in the dose range studied.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary evidence to support the clinical efficacy of nivolumab at a dose of 3 mg/kg administered intravenously every 2 weeks for the treatment of unresectable or metastatic melanoma who are refractory to ipilimumab, and to BRAF inhibitors if indicated, is derived primarily from data from Trial CA209037. Supportive results were derived from Trial CA209003.

The primary safety data used to characterize the safety profile of nivolumab is derived from the All Treated Population from Trial CA209037. Safety data from melanoma and non-melanoma patients in Trial CA209003 was used to supplement the safety review. Table 2 lists the clinical trials included in the BLA submission.

Table 2: Tabular Listing of Clinical Trials

Study	Purpose	Population	Study Design	Sites N	Countries	Subjects N
CA209037	Efficacy, safety	Unresectable or metastatic melanoma who have progressed on or after anti-CTLA-4 therapy, and if BRAF V600 mutation positive to also have progressed on or after a BRAF inhibitor	Phase 3, randomized, open-label	90	US, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom	370[a]
CA209003/ MDX1106-03	Safety, efficacy, PK	Metastatic NSCLC, CRC, melanoma, RCC (clear cell), or HRPC	Phase 1 dose escalation	13	USA	103[b]

CA209006	Safety, efficacy	Unresectable or metastatic melanoma who had progressive disease after at least one prior systemic therapy	Phase 1 study	N/A	USA	90[c,d]
CA209001/ MDX1106-01	Safety, efficacy, PK	Refractory or relapsed NSCLC, CRC, malignant melanoma, RCC (clear cell), or HRPC	Phase 1 dose escalation	4	USA	39
CA209063[d]	Safety, efficacy	Advanced or metastatic squamous cell NSCLC progressed during or after platinum doublet based chemotherapy and at least one additional systemic therapy	Phase 2, single arm study	27	USA, France, Germany, Italy	117
CA209010[e]	Safety, efficacy, PK	Progressive, advanced or metastatic RCC (clear cell) progressed on prior anti-angiogenic therapy	Phase 2, randomized, blinded, dose-ranging study	39	4 countries	167

Abbreviations: CRC, colorectal adenocarcinoma; HRPC, hormone-refractory prostate adenocarcinoma; N/A, not available; NSCLC, non-small cell lung cancer; PK, pharmacokinetic trial; RCC, renal cell carcinoma; USA, United States.
[a] 268/370 patients treated with nivolumab.
[b] 17/103 patients treated with nivolumab at a dose of 3 mg/kg Q2W.
[c] 56/90 patients treated with nivolumab with progression after prior ipilimumab.
[d] safety summary data submitted
[e] ECG analysis submitted

Reviewer Comment:
The primary evidence of efficacy and safety is provided by Trial CA209037. Although a randomized trial, the interim analysis of efficacy is based on a non-comparative analysis of 120 patients in the nivolumab group. The safety analysis is based on 370 treated patients, 268 in the nivolumab group and 102 in the investigator's choice group.

5.2 Review Strategy

The FDA clinical BLA review consisted of two primary clinical reviewers, one primary reviewer of safety and one primary reviewer of efficacy. The primary clinical reviewer of safety was also responsible for synthesis and documentation of the overall conclusions of the application.

The BLA submission contained Trial CA209037, a randomized, open-label, Phase 3, multi-center trial of nivolumab vs. investigator's choice in advanced unresectable or metastatic melanoma patients who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy. A total of 631 patients were enrolled into

Trial CA209037, of which 272 patients were randomized to the nivolumab arm and 133 patients to the investigator's choice arm.

The clinical review of efficacy focuses on the first 120 patients treated with nivolumab who had at least 6 months of follow-up from study CA209037 in support of the proposed indication, including a detailed review and analysis of data including the clinical study report (CSR), case report forms (CRFs), and datasets in consultation with the FDA statistical review team. The Applicant provided efficacy data for the first 60 patients randomized to investigator's choice as a reference. The efficacy review was supplemented with an evaluation of a subset of patients with melanoma treated on study CA209003. The following efficacy endpoints are analyzed: investigator-assessed confirmed objective response rate (ORR), BIRC assessed confirmed ORR, duration of response, PFS, and OS.

The clinical review of safety focused on 370 treated patients treated in Trial CA209037 [268 in the nivolumab group and 102 in the investigator's choice group treated with either dacarbazine (n=45) or carboplatin/paclitaxel therapy (n=57)] with additional analyses focused on select adverse events (AEs) including immune-mediated AEs with nivolumab [e.g., deaths, non-fatal serious adverse events (SAEs), AEs leading to treatment modifications], including a detailed review and analysis of data including the CSR, CRFs, narratives, and datasets.

The clinical review of safety was supplemented with an evaluation of 306 patients with melanoma (107 patients) and non-melanoma indications (199 patients) treated on Trial CA209003, in which, as of the cutoff date of February 4, 2013, 20 (6.5%) patients are still receiving treatment, and 111 (36.3%) patients are in survival follow up. The clinical review of safety also included the 90-day safety update. The Applicant was queried on the occurrence of specific immune-mediated AEs and provided information on the specific AEs from other completed and ongoing studies with nivolumab from the Applicant safety database, which included a total of 1524 patients from studies CA209037, CA209038, CA209066, MDX1106-03, CA209063, CA209017, CA209057, and CA209025 with a data cut-off on July 29, 2014 (Response to FDA Information Request dated November 10, 2014).

The clinical review included the following:

- Review of the current literature on melanoma epidemiology, and treatment, including other immune-mediated therapies
- Review of Applicant submitted trials CA209037 and CA209003, including clinical study reports, protocols, protocol amendments
- Review and assessment of Applicant analysis of nivolumab efficacy and safety, for evaluation of Applicant's claims
- Review of datasets submitted as SAS transport files
- Review of patient narratives of serious adverse events and deaths
- Review of meeting minutes conducted during drug development

- Assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Risk Management Plan, and proposed labeling for nivolumab
- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Pharmacology, Biostatistics, and CMC
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Review and evaluation of proposed labeling

Reviewer Comment:
As requested by the FDA, the Applicant submitted the 4-month safety update as a 90-day safety update. Safety data were reviewed in order to determine whether the proposed safety database will be sufficient to evaluate the immune-mediated AEs on the tolerability of nivolumab.

5.3 Discussion of Individual Studies/Clinical Trials

PROTOCOL ID: CA209037 (No. 4/ March 28, 2014)

Clinical Trial Title

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
[CheckMate 037: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 037]

Study Sites

370 subjects were treated at 90 sites in 14 countries (US, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom).

Objectives

- Primary Objectives:
    - To estimate the objective response rate (ORR) in the nivolumab treatment group (noncomparative assessment of the first 120 nivolumab-treated subjects with a minimum of 6 months follow-up)
    - To compare the overall survival (OS) of nivolumab to investigator's choice (All Randomized population).

- Secondary Objectives:
    - To compare the progression-free survival (PFS) of nivolumab to investigator's choice in subjects with advanced melanoma.
    - To evaluate whether PD-L1 expression is a predictive biomarker for ORR and OS.
    - To evaluate HRQoL as assessed by European Organisation for Research and Treatment of Care (EORTC) QLQ-C30.
- Exploratory Objectives:
    - To assess the overall safety and tolerability of nivolumab and investigator's choice.
- To characterize the pharmacokinetics (PK) of nivolumab and explore exposure-response relationships with respect to safety and efficacy.
- To characterize the immunogenicity of nivolumab.
- To explore potential biomarkers associated with clinical response to nivolumab by analyzing tumor tissue specimens and serum for proteins.
- To assess the effects of natural genetic variation (single nucleotide polymorphism [SNPs]) in select genes including but not limited to PD-1, PD-L1, PD-L2 and CTLA-4 on clinical endpoints and/or on the occurrence of adverse events (AEs).
- To assess changes in health status in treatment groups by the EuroQoL EQ-5D both on treatment and during the survival follow-up period.

Study Design

Trial CA209037 is a randomized, open-label, multicenter, study designed to evaluate nivolumab monotherapy vs. investigator's choice (dacarbazine or carboplatin and paclitaxel) in advanced (unresectable or metastatic) melanoma patients who have progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy. Patients were randomized in a 2:1 ratio and stratified by PD-L1 status with a verified immunohistochemistry (IHC) assay (PD-L1 expression ≥ 5% of tumor cells membrane staining in a minimum of 100 evaluable tumor cells vs. < 5% cutoff), BRAF status (wildtype vs. BRAF V600 mutation positive), and prior anti-CTLA-4 best response [complete response (CR); partial response (PR); stable disease (SD) vs. progressive disease (PD); CR, PR, SD, and PD as defined by RECIST].

This study consisted of three phases: screening, treatment and follow-up. Treatment was continued until disease progression, or discontinuation of study therapy in subjects receiving nivolumab beyond progression, discontinuation due to toxicity, or other reasons for discontinuation. During the follow-up phase (after patients discontinued therapy) patients had two follow-up visits for safety assessments and collection of PK and immunogenicity samples; patients were followed for survival every 3 months. Patients were not permitted to crossover.

Study Population *(key eligibility criteria)*

Subjects at least 18 years of age, male or female, who signed the Informed Consent Form (ICF) and who met the following main disease criteria upon screening were included in the study:

Inclusion Criteria for Disease State and Previous Treatment

- Histologically confirmed Stage III (unresectable) or Stage IV melanoma.
- Classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate by a pre-treatment recent core, excision or punch biopsy from an unresectable or metastatic site. No intervening systemic therapy should be administered between the time of biopsy and randomization.
- Objective evidence of disease progression (e.g., clinical or radiological) during or after at least one (V600 wildtype) or at least two (V600 mutation positive) prior treatment regimens for advanced melanoma.
    - Subjects BRAF wildtype: evidence of progression of disease (PD) post (during or following) treatment with anti-CTLA-4 containing therapy for advanced melanoma and those subjects who have received another treatment regimen must have objective evidence of PD during or following at least 1 cycle of treatment for advanced melanoma.
    - Subjects BRAF V600 mutation positive: objective evidence of PD post treatment with anti-CTLA-4 containing therapy and BRAF inhibitor therapy for advanced melanoma, in any sequence or in any combination.
- Prior chemotherapy or immunotherapy (tumor vaccine, cytokine, or growth factor given to control the cancer) was completed at least 4 weeks before study drug administration, and all AEs have either returned to baseline or stabilized.
- Prior anti-CTLA-4 therapy was completed at least 6 weeks before study drug administration.
- Prior radiotherapy completed at least 2 weeks prior to first dose of study drug administration.
- Measurable disease by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1 criteria.
- Eastern Cooperative Oncology Arm (ECOG) performance status of 0 or 1.

Exclusion Criteria

Subjects who met any of the following main exclusion criteria were to be excluded from the study:

Target Disease Exceptions

- Active brain metastasis or leptomeningeal metastasis: Subjects with brain metastases were eligible if these were treated, and had no evidence of progression for at least 8 weeks prior to start of study treatment by MRI (except where contraindicated in which case CT scan was acceptable) and did not

require immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone or equivalent) for at least 2 weeks prior to study drug administration.
- Ocular melanoma.
- Subjects whose melanoma BRAF status was unknown.

Medical History and Concurrent Diseases
- Subjects with active, known, or suspected autoimmune disease
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first dose of study drug. Corticosteroids with minimal systemic absorption (for example topical or inhalational), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, were permitted in the absence of active autoimmune disease.
- Prior therapy with anti-PD-1, anti-PD-1 ligand 1- or 2- (PD-L1 or PD-L2), or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways except for anti-CTLA-4 therapy as described above.
- Prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel.
- Subjects with previous malignancies (except nonmelanoma skin cancers, in situ bladder cancer, gastric or colon cancers, cervical cancers/dysplasia, or breast carcinoma in situ) were excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy was anticipated to be required during the study period.

Anti-CTLA-4 Therapy Related Drug Reactions
Subjects with a known history of the following anti-CTLA-4 therapy related adverse reactions based on the CTCAE v4.0 criteria:
- Grade 4 anti-CTLA-4 therapy related adverse reaction except resolved nausea, fatigue, infusion reactions or endocrinopathies where clinical symptoms were able to be controlled with appropriate hormone replacement therapy. Grade 3 anti-CTLA-4 therapy related adverse reactions must have resolved or been controlled within 12 weeks.
- Any ≥ Grade 2 eye pain or reduction of visual acuity that did not respond to topical therapy and did not improve to ≤ Grade 1 severity within 2 weeks of starting topical therapy or that required systemic treatment.
- Any ≥ Grade 3 sensory neurologic toxicity.
- Any Grade 4 laboratory abnormalities, except aspartase aminotransferase (AST), alanine aminotransferase (ALT) or total (T.) bilirubin;
    1) AST or ALT > 10 x upper limit of normal (ULN)
    2) Total bilirubin > 5 x ULN
- Subjects who required infliximab or other immune suppressants including mycophenolic acid for management of drug-related toxicities

Treatment Plan

BMS-936558 (nivolumab) is dosed intravenously over 60 minutes at 3 mg/kg every 2 weeks (14 days) (Q2W) or investigator's choice [choice of either dacarbazine dosed intravenously between 30 to 60 minutes at 1000 mg/m^2 every 3 weeks (21 days) or carboplatin (AUC 6) dosed intravenously over 30 minutes and paclitaxel 175mg/m^2 dosed intravenously over 180 minutes every 3 weeks (21 days)].

Dose Modification and Management Algorithms

Dose reductions were not permitted. The Applicant developed management algorithms to assist investigators in assessing and managing the following groups of AEs: gastrointestinal, renal, pulmonary, hepatic, endocrinopathies, skin, and neurological.

Refer the Appendix 9.4 for management algorithms for select AEs.

Monitoring Plan

Radiographic assessments were performed at 9 weeks and then every 6 weeks thereafter for the first 12 months, then every 12 weeks until disease progression or treatment discontinuation. Tumor responses were assessed by blinded independent central review (BICR) per RECIST v.1.1 for the primary endpoint of the trial. Patient management on the clinical trial was based on investigator assessment per RECIST v.1.1.; however, patients treated with nivolumab with progressive disease by RECIST v.1.1 as assessed by the investigator were allowed to remain on study if they were deriving investigator-assessed clinical benefit and were tolerating the study drug. The investigator assessment included whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. Patients were re-consented prior to continuing nivolumab and were to discontinue therapy upon further evidence of progression, defined as an additional 10% or greater increase in tumor from time of initial progression (including all target lesions and new measurable lesions). Patients who continued treatment beyond initial investigator-assessed, RECIST 1.1-defined progression were considered to have investigator-assessed progressive disease at the time of the initial progression event for purposes of the analyses.

A prospectively defined BICR which consisted of three radiologists (2 readers plus an adjudicator if needed) was used for the primary analysis of ORR as well as the analysis of progression-free survival (PFS) (see below for further details regarding the BICR).

Safety assessments were conducted at the screening visit, on-study, and follow-up. Safety assessments at screening included physical examination, vital signs, oxygen saturation, physical measurements, ECOG performance status, assessments of baseline signs and symptoms, concomitant medication collection, laboratory tests, urinalysis, and pregnancy test. On-study safety assessments were conducted at each cycle and included physical examination, vital signs, oxygen saturation, physical measurements, ECOG performance status, AE and SAE assessments, review of

concomitant medications, laboratory tests, pregnancy test, and immnunogenicity test. The same safety assessments were conducted at two follow-up visits, the first visit at 30 days after the last dose of the study drug and the second visit at 84 days from follow-up visit 1.

Blinded Independent Central Review

The primary endpoint (ORR) and secondary endpoint (PFS) were evaluated by BICR per RECIST v.1.1. The BICR consisted of three radiologists (two readers plus an adjudicator if needed). As stated in the independent review charter, the independent radiologic review was conducted in three sequential stages:

- Timepoint-by-timepoint imaging response evaluation
- Global radiology analysis
- Adjudication, if applicable

Two reviewing radiologists performed the initial timepoint by timepoint tumor evaluations and were provided limited clinical data including radiation or surgery performed prior to study entry (including date, site and/or radiation field and lesion progression status, if known).

For the global radiology analysis, the two reviewing radiologists were presented with all lesion assessments and timepoint responses and any available on-study clinical data including any on-study procedures, tumor-directed radiotherapy or surgery, cytology or biopsy reports, and dates of initiation of subsequent systemic anti-cancer therapy.

If any of the response evaluations after the global radiology analysis, including best overall response, confirmed best overall response, date of first response, or date of progression were not identical between the two readers, an adjudication by a third radiologist was performed. The adjudicator reviewed all the results from both initial readers and indicated which primary reviewer's results they believe most accurately represents the above variables for the case.

Adverse Event Collection

Per protocol, SAEs and all non-serious AEs (not only those deemed to be treatment-related) were to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Analysis Populations

- All Enrolled Subjects: Subjects who signed an informed consent form and were registered into the IVRS.
- Randomized Subjects: Subjects who were randomized to any treatment group in the study.

Two different analysis populations used:
    - All Randomized Subjects: This dataset will be used for analyses of study conduct and study population.
    - ORR population: All randomized subjects with an opportunity for at least 6 months of follow-up at the time of ORR analysis timepoint. This dataset will be used for study population and some efficacy analyses.

  Subject's follow-up time is defined here as the time between randomization date and database cutoff date regardless of subject disposition (i.e., intent-to-treat population). The clinical database cutoff date will occur when the first 180 randomized subjects have an opportunity to be followed for at least 6 months.
- All Treated Subjects: Subjects who received at least one dose of nivolumab, dacarbazine, paclitaxel or carboplatin. This is the primary dataset for analyses of exposure and safety. Safety and exposure will include all treated subjects in the database at the time ORR is analyzed and will not be restricted based on a 6-month minimum follow-up.
- Treated subjects among ORR population: This is the primary dataset for ORR efficacy analysis (restricted to subjects treated with nivolumab)
- PD-L1 Measurable Subjects in ORR population: Subjects with a measurable PD-L1 expression result (excludes indeterminate and unknown) among ORR population

Statistical Considerations

The sample size of the study accounts for the co-primary efficacy endpoints: ORR (per BIRC) and OS with a two-sided alpha allocation of 0.1% and 4.9% respectively. The ORR is defined as the number of subjects with a confirmed CR or PR divided by the number of subjects. OS is defined as the time between the date of randomization and the date of death. Formal analyses of ORR and OS will be conducted at different timepoints with ORR being analyzed first followed by interim and final OS analyses. Approximately 390 patients will be randomized to the two treatment groups in a 2:1 ratio.

The primary analysis of ORR in the nivolumab treatment group will be performed when the first 120 patients treated with nivolumab (i.e., approximately 180 treated subjects in total: 120 in the nivolumab treatment group and 60 in the investigator's choice treatment group) will have a minimum follow up of 6 months. BICR- determined ORR in the nivolumab group will be estimated and its corresponding 95% exact two-sided CIs will be calculated using the Clopper Pearson method.

Duration of response (DOR) will be evaluated for responders (i.e. subjects with confirmed CR or PR) only. DOR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by the BICR per RECIST 1.1, or death due to any cause, whichever occurs

first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they will be censored for the primary definition of PFS.

At the time of formal ORR analysis, only descriptive analysis of OS will be produced (i.e., no formal interim comparison of OS will be performed).

The formal comparison of OS will be performed on all randomized subjects. At least 260 deaths will be required to provide approximately 90% power to detect a HR of 0.65, corresponding to a median OS of 8 vs. 12.3 months (4.3 month difference) for the investigator's choice and nivolumab treatment groups, respectively, with an overall two-sided type I error of 4.9%. One formal OS interim analysis will be conducted when at least 169 deaths (i.e., 65% of total events) have been observed.

PFS will be analyzed at the time of the OS formal analysis, on all randomized subjects. Hierarchical hypothesis testing will be used for the PFS endpoint, i.e., PFS formal comparison will only occur if the OS comparison is statistically significant. At the time of formal ORR analysis, only descriptive analysis of PFS will be produced (i.e., no formal interim comparison of PFS will be performed). PFS is defined as the time from randomization to the date of the first documented progression, as determined by the BIRC per RECIST 1.1, or death due to any cause, whichever occurs first. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy (including tumor-directed radiotherapy and tumor-directed surgery) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Protocol Amendments

The Applicant submitted 10 amendments to Protocol CA209037. Key revisions are provided below:

- Amendment 06 (March 13, 2013): Updated Summary of Safety section to include new preliminary reproductive toxicology data that was distributed as a Non-clinical Expedited Safety Report and included changes to the guidance on contraception.
- Amendment 08 (April 29, 2013): Modified the number of prior therapies allowed in the eligibility criteria (from two prior therapies to one prior therapy); required confirmation of objective response; clarified that subjects receiving palliative radiotherapy would be classified as having unequivocal progression.
- Amendment 09 (October 29, 2013): Updated the study design to perform an adequately powered statistical comparison of the co-primary endpoint of Objective Response Rate (ORR) at an earlier timepoint while maintaining the

power for statistical comparison of the other co-primary endpoint of Overall Survival (OS): formal analyses of ORR and OS will be conducted at different timepoints with ORR being analyzed first followed by interim and final OS analyses.

- Amendment 10 (March 28, 2014): Modified the co-primary endpoint to allow a non-comparative estimation of ORR on the nivolumab arm; the OS co-primary endpoint will be tested using 4.9% significance level.

Reviewer Comments:

1. *Trial CA209037 was modified to allow a non-comparative estimation of ORR in the nivolumab arm. However, randomization allows evaluation of the efficacy and safety of nivolumab vs. investigator's choice chemotherapy. Randomization is useful in minimizing selection bias.*
2. *Trial CA209037 was an open-label trial with a potential for assessment bias. The prospective blinded independent central review for responses is useful in minimizing assessment bias.*
3. *Trial CA209037, designed as a multicenter and multi-investigator trial provides a better basis for the subsequent generalization of its findings. In the interim analysis population analyzed, out of 167 patients in the efficacy population, 74 patients were treated in the USA, 52 in the nivolumab group and 22 in the investigator's choice group; and out of 370 patients in the safety population, 146 patients were treated in the USA, 103 in the nivolumab group and 43 in the investigator's choice group.*

PROTOCOL ID: CA209003

Trial CA209003 was a Phase 1, open-label, multi-center, multi-dose, dose-escalation study of single-agent nivolumab across multiple tumor types. The primary objective was to assess the safety and tolerability of multiple doses of nivolumab in patients with selected advanced or recurrent malignancies, including metastatic castration-resistant prostate cancer, renal cell carcinoma, colorectal adenocarcinoma, malignant melanoma, and non-small cell lung cancer in up to 290 patients. The tumors were advanced (non-resectable) or recurrent and progressed since last anti-tumor therapy, and for which no alternative, curative standard therapy existed. The patients with melanoma treated on this study had advanced or recurrent disease after at least one and up to five prior therapies, but could not have received prior anti-PD-1, PD-L1/L2 or anti-CTLA-4 antibody therapy.

Tumor response was by investigator as per RECIST v.1.0 and disease assessments were performed every 8 weeks. Patients were treated until confirmed disease progression, confirmed CR, unacceptable toxicity, or up to 12 cycles (96 weeks) of therapy. Patients who entered the follow-up period with ongoing disease control (CR, PR, or SD) and had disease progression within one year were allowed to be retreated

for up to 48 weeks. Nivolumab dose levels were 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg or 10 mg/kg administered every 2 weeks as an intravenous infusion over 1 hour.

6 Review of Efficacy

Efficacy Summary

The BLA contained data from Trial CA209037, entitled "A Randomized, Open-Label, Phase 3 Trial of BMS-936558 (Nivolumab) Versus Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy". The trial is an international, open-label, randomized (2:1), controlled clinical trial of nivolumab at a dose of 3mg/kg every 2 weeks compared with investigator's choice chemotherapy (dacarbazine 1000mg/m^2 every 3 weeks or carboplatin AUC 6 and paclitaxel 175mg/m^2 every 3 weeks) in patients with advanced melanoma who have progressed following treatment with ipilimumab, or ipilimumab and a BRAF inhibitor for patients with BRAF mutated melanoma. The co-primary endpoints of the trial are overall response rate (ORR) by blinded independent central review (BICR) according to RECIST v1.1 and overall survival (OS) of patients in the nivolumab group compared to the investigator's choice group. Key secondary endpoints include comparison of the progression-free survival (PFS) between the two groups and an evaluation of whether PD-L1 expression is a predictive biomarker for ORR and OS. The Applicant has submitted, in agreement with FDA, an interim analysis of trial CA209037 which includes the analysis of ORR and duration of response (DOR) for the first 120 patients treated with nivolumab after at least 6 months of follow up (referred to as the *treated ORR population*) in support of the proposed indication. The Applicant has also submitted, at the request of FDA, descriptive, non-comparative analyses of PFS and OS.

The BLA also includes results from analyses of patients with melanoma treated on study CA209003, "A Phase 1 Open-Label, Multicenter, Multidose, Dose Escalation Study of BMS-936558 (MDX-1106) in Subjects with Selected Advanced Recurrent Malignancies". The efficacy review includes a review of 87 patients with advanced melanoma on study CA209003 who received nivolumab at or below the dose proposed for the indication (i.e., 0.1mg/kg, N=17; 0.3mg/kg, N=18; 1mg/kg, N=35, and 3mg/kg, N=17) as supportive data for ORR and DOR.

In Trial CA9209037, the results from the first 120 patients treated with nivolumab in the treated ORR population demonstrated an ORR of 31.7% (95% CI: 23.5, 40.8). Of the 38 patients with an objective response, the median duration of response was not reached (range 1.4 to 10+ months). Responses were ongoing in 87% of patients at the time of data cut-off with durations of response ranging from 2.6+ to 10+ months, including 13 patients with ongoing responses of 6 months or longer.

In the descriptive analysis of PFS as assessed by BICR in the ORR population, the median PFS was 4.7 months (95% CI: 2.3, 6.5) in the nivolumab group and 4.2 months

(95% CI: 2.1, 6.3) in the investigator's choice group. The median OS was not reached in the nivolumab group (95% CI: 11.5 months, NR) and was 11.8 months (95% CI: 7.8, NR) in the investigator's choice group.

The treatment effect of nivolumab appeared consistent across all subgroups in the exploratory subgroup analysis of ORR. Objective responses were observed in patients with and without BRAF mutations. In addition, the ORR in the 87 patients with melanoma treated with nivolumab on the dose-escalation trial CA209003 at doses at or below 3mg/kg every 2 weeks was 33.3% (95% CI: 23.6, 44.3). The median DOR was 22.9 months (95% CI: 12.9, NR) with a range of 4.2 to 26.6+ months.

The ORR and DOR of nivolumab demonstrate anti-tumor activity that is reasonably likely to predict clinical benefit for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, a patient population with a serious and life-threatening disease for which there are no FDA-approved therapies with proven clinical benefit. FDA recently granted accelerated approval for pembrolizumab, another anti PD-1 monoclonal antibody, for the same indication but studies to confirm clinical benefit are underway, so this is not considered available therapy for this patient population.

6.1 Indication

The Applicant proposes the following indication for the nivolumab label.

"OPDIVO is a programmed death-1 (PD-1) (b) (6) indicated for the treatment of unresectable or metastatic melanoma in patients previously treated with ipilimumab, (b) (6)

6.1.1 Methods

The Applicant submitted two clinical trials to support the efficacy of nivolumab for this BLA review, Trial CA209037 and Trial CA209003. The data from these two trials are not pooled given the differences in patient selection criteria, and trial design and conduct, but the tumor response and duration of response data from patients treated on Trial CA209003 who have a longer duration of follow up than patients on Trial CA209037are supportive of the efficacy of nivolumab. Both trials are described in detail in Section 5.3.

6.1.2 Demographics

The interim efficacy analysis includes a single-arm analysis of ORR in the first 120 patients treated with nivolumab in Trial CA209037 with at least 6 months of follow-up, referred to as the *treated ORR population*. The results for the 47 patients treated with investigator's choice chemotherapy are presented in a non-comparative manner to demonstrate the ORR for conventional chemotherapy in this patient population. Overall,

the demographics were well-balanced as shown in Table 3, except that a greater proportion of patients younger than 65 were enrolled in the nivolumab (68%) as compared with the investigator's choice group (53%) and more patients in the nivolumab group had an elevated LDH (56%) compared to patients in the investigator's choice group (53%). The majority of patients were male (65% in the nivolumab group and 64% in the investigator's choice group), White (98% and 96%), and treated in the US (43% and 47%). At the time of enrollment, the majority of patients had an ECOG performance status of 0 (58% and 55%), M1c disease (76% and 74%), and no prior history of brain metastases (82% and 85%). Twenty-two percent of patients in the nivolumab and 23% of patients in the investigator's choice group had BRAF V600 mutations. All patients received prior therapy with ipilimumab, none in the adjuvant setting, and 37% of patients in the nivolumab and 34% in the investigator's choice group had prior benefit from ipilimumab defined as a best response of complete response (CR), partial response (PR) or stable disease (SD). All of the patients with BRAF mutations received therapy with a BRAF inhibitor.

Table 3 summarizes the demographics and baseline disease characteristics for patients in the treated ORR population

Table 3: Demographics and Baseline Characteristics Treated ORR Population

	Nivolumab N=120 n (%)	**Investigator's choice N=47 n (%)**
Gender		
Female	42 (35)	17 (36)
Male	78 (65)	30 (64)
Age		
Median, years	58	64
Range, years	25-88	29-84
<65	82 (68)	25 (53)
>=65 and <75	24 (20)	15 (32)
>=75	14 (12)	7 (15)
Countries		
United States	52 (43)	22 (47)
Other	19 (16)	8 (17)
United Kingdom	13 (11)	7 (15)
Italy	10 (8)	6 (13)
Belgium	14 (12)	1 (2)
Germany	12 (10)	3 (6)
Race		
White	118 (98)	45 (96)
Asian	2 (2)	0
Other	0	1 (2)
Black or African American	0	1 (2)
ECOG PS		
0	70 (58)	26 (55)

	Nivolumab N=120 n (%)	Investigator's choice N=47 n (%)
1	50 (42)	20 (43)
2*	0	1 (2)
BRAF V600 mutation subtype		
Mutant	26 (22)	11 (23)
Wild-type	94 (78)	36 (77)
LDH[a]		
Elevated	67 (56)	20 (43)
Normal	53 (44)	27 (57)
Disease stage		
Stage III	5 (4)	0
M1a	8 (7)	2 (4)
M1b	16 (13)	10 (21)
M1c	91 (76)	35 (74)
History of brain metastases		
Yes	21 (18)	7 (15)
No	99 (82)	40 (85)
Melanoma subtype		
Cutaneous	86 (72)	40 (85)
Mucosal	10 (8)	2 (4)
Acral	6 (5)	2 (4)
Other: unknown primary	8 (7)	1 (2)
Other	10 (8)	2 (4)
PD-L1 status[b]		
Positive	55 (46)	22 (47)
Negative/indeterminate	65 (54)	25 (53)
Prior systemic chemotherapy regimens in metastatic setting		
1	39 (32)	11 (23)
2	60 (50)	29 (62)
3 or more	21 (18)	7 (15)
Prior ipilimumab benefit[c]		
Yes	44 (37)	16 (34)
No	76 (63)	31 (66)
Prior ipilimumab therapy		
Yes	120 (100)	47 (100)
Adjuvant	0	0
Prior adjuvant therapy		
Yes	18 (15)	6 (12.8)
No	102 (85)	41 (87)
Prior BRAF inhibitor		
Yes	26 (22)	11 (23)
No	94 (78)	36 (77)
Prior immunotherapy in metastatic setting[d]		
Yes	17 (14)	10 (21)
No	103 (86)	37 (79)

Source: ADSL.xpt, CM.xpt, ADCM.xpt; SUPPMH.xpt, Applicant Response to 11/7/2014 FDA Information Request
[a] LDH=lactic dehydrogenase
[b] Defined as ≥5% tumor cell membrane expression of PD-L1 by verified BMS immunohistochemistry assay

[c] Defined as best overall response with ipilimumab of CR, PR or SD
[d] Does not include ipilimumab

Reviewer Comments:

1. *There was a discrepancy between anti-CTLA4 benefit listed in the IVRS system used to stratify patients on randomization and data in the case report forms (CRFs) for eight patients on the nivolumab group (76 patients with "no" benefit listed in IVRS and 80 with "no" benefit in CRF and 44 patients with "yes" in IVRS and 40 patients with "yes" benefit in CRF) and two patients on the investigator's choice group (31 patients with "no" benefit listed in IVRS and 32 listed with "no" benefit in CRF and 16 patients with "yes" benefit in IVRS and 15 patients with "yes" benefit in CRF). This is not expected to have a significant impact on the efficacy analysis of ORR for this BLA as these are exploratory subgroup analyses. Also, the clinical significance of prior anti-CTLA4 therapy benefit as defined in the protocol is unclear.*
2. *One patient had an ECOG PS of 2 in the investigator's choice group which constituted a protocol violation (see eligibility criteria in Section 5.3).*

Table 4 and Table 5 summarize prior anti-cancer therapies received in the adjuvant and advanced or metastatic setting, respectively, by patients in the treated ORR population. Patients may have received more than one regimen or multiple courses of the same regimen in the adjuvant or advanced/metastatic setting. As required by inclusion criteria, all patients were previously treated with anti-CTLA-4 therapy (all patients received ipilimumab as their anti-CTLA-4 therapy). There were no significant differences between the groups except that more patients in the nivolumab group were reported to have received chemotherapy as adjuvant therapy.

Table 4: Prior Adjuvant Anti-cancer Therapy

Therapy	Nivolumab N=120 n (%)	Investigator's choice N=47 n (%)
All adjuvant therapy	18 (15)	6 (13)
Immunotherapy		
interferon	15 (12)	6 (13)
interleukin 2	2 (2)	0
sargramostim	0	1 (2)
investigational immunotherapy	1 (<1)	0
Chemotherapy/Other		
temozolomide	3 (2)	0
dacarbazine	1 (<1)	0
bevacizumab	1 (<1)	0
cisplatin	1 (<1)	0
docetaxel	1 (<1)	0
investigational antineoplastic	1 (<1)	0

Source: CM.xpt, ADCM.xpt

Table 5: Prior Anti-cancer Therapy in Advanced or Metastatic Setting

Therapy	Nivolumab N=120 n (%)	Investigator's choice N=47 n (%)
All therapy in advanced or metastatic setting	120 (100)	47 (100)
Immunotherapy		
ipilimumab*	120 (100)	47 (100)
interleukin 2	9 (8)	5 (11)
interferon	9 (8)	2 (4)
sargramostim	0	1 (2)
T cell infusion	1 (<1)	0
investigational immunotherapy	3 (2)	2 (4)
BRAF or MEK inhibitor		
vemurafenib	22 (18)	9 (19)
dabrafenib	4 (3)	2 (4)
trametinib	1 (<1)	1 (2)
Chemotherapy/Other		
dacarbazine	33 (28)	15 (32)
temozolomide	14 (12)	3 (6)
investigational antineoplastic	5 (4)	6 (13)
fotemustine	3 (2)	4 (8)
cisplatin	3 (2)	1 (2)
docetaxel	2 (2)	2 (4)
paclitaxel	3 (2)	1 (2)
cyclophosphamide	3 (2)	0
vinblastine	2 (2)	1 (2)
bevacizumab	1 (<1)	1 (2)
carboplatin	1 (<1)	1 (2)
fludarabine	2 (2)	0
antineoplastic	1 (<1)	0
axitinib	1 (<1)	0
melphalan	1 (<1)	0
vindesine	1 (<1)	0

Source: CM.xpt, ADCM.xpt
* 14 patients received more than one course of ipilimumab (12 in the nivolumab group and 2 in the investigator's choice group)

Reviewer Comment:
As per datasets above for Table 5, all patients received therapy in the metastatic setting; options on the CRF for settings of prior therapy included adjuvant, metastatic, and neo-adjuvant. No patients received systemic therapy in the neo-adjuvant setting.

6.1.3 Subject Disposition

At the time of data cutoff, a total of 631 patients had been enrolled in 90 sites in 14 countries (US, Austria, Belgium, Brazil, Canada, Denmark, France, Germany, Israel, Italy, Netherlands, Spain, Switzerland, and United Kingdom). The enrollment period was from December 21, 2012 (first patient first visit) until January 10, 2014 (last patient first visit).

Of the 631 enrolled patients, 405 (64%) were randomized (272 in the nivolumab group and 133 in the investigator's choice group), and 370 (59%) were treated with study drug (268 in the nivolumab group and 102 in the investigator's choice group). The primary population for the efficacy evaluation of ORR for this BLA is referred to as the *treated ORR population*. The interim analysis for this BLA was performed when the first 120 patients randomized and treated with nivolumab had a minimum follow-up of 6 months. The ORR population consists of 122 patients as two patient were randomized to nivolumab but were not treated. The ORR population is used for the descriptive analyses of PFS and OS. Table 6 summarizes the populations in trial CA209037 used in the analyses.

Table 6: Analyses Populations in Trial CA209037

Population	Nivolumab Group	Investigator's Choice Group	Total
Enrolled: all subjects who signed an informed consent and were registered			631
All Randomized Population:	272	133	405
All Treated Population: All subjects treated with at least one dose of study drug	268	102	370
ORR Population: All subjects randomized to either treatment group with at least 6 months of follow-up at the time of the ORR analysis, which occurred when the first 120 nivolumab-treated subjects had a minimum of 6 months of follow-up.	122	60	182
Treated ORR Population: All subjects who received at least one dose of treatment (nivolumab or investigator's choice) and had at least 6 months of follow-up at the time of the ORR analysis. The primary endpoint analysis or ORR was restricted to subjects treated with nivolumab.	120	47	167

Source: Modified from CA209037 Clinical Study Report, Table 5.2-1.

Two hundred and twenty-six (36%) patients were not randomized as summarized in Table 7. The most common reason for screen failure was that the patient no longer met study criteria (88%), followed by withdrawal of consent (8%). Table 7 summarizes the screen failures for all enrolled patients.

Table 7: Reasons for Screen Failures in All Enrolled Population

Patients	N (%)
Total enrolled	631 (100)
Randomized	405 (64)
Not randomized	226 (36)
Reason not randomized	
Subject no longer meets study criteria	198 (88)
Subject withdrew consent	17 (8)
Other	4 (2)
Death	3 (1)
Administrative reason by sponsor	1 (<1)
Adverse event	1 (<1)
Lost to follow-up	1 (<1)
Poor/non-compliance	1 (<1)

Source: ADSL.xpt, IE.xpt

Table 8 summarizes the eligibility criteria not met by the 198 patients who were enrolled but not randomized for failure to meet eligibility criteria. The most common (≥10%) reasons for screen failure were brain metastases (49%), ECOG status >1 (14%), and no pretreatment biopsy (13%). Note that a patient could have more than one reason as a screen failure and therefore, be counted more than once.

Table 8: Patients Enrolled, Not Randomized by Failure to Meet Eligibility Criteria

Inclusion/Exclusion Criteria Not Met	N (%)
Total Not Randomized	**198 (88%)**
Exclusion criteria 1A: Active brain metastases or leptomeningeal metastasis	97 (49)
Inclusion criteria 2A: ECOG ≤1	28 (14)
Inclusion criteria 2D: Availability of pretreatment biopsy for PD-L1 status	25 (13)
Inclusion criteria 2J: Adequate baseline laboratory values	18 (9)
Inclusion criteria 1B: Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests / including completion of quality of life questionnaires and other requirements of the study	15 (8)
Inclusion criteria 2C: Measurable disease by CT or MRI per RECIST 1.1 criteria.	11 (6)
Inclusion criteria 2F1A: BRAF wildtype: Objective evidence of PD post treatment with anti-CTLA-4 containing therapy / Relapse ≤ 6 months of last dose of anti-CTLA-4 adjuvant treatment for completely resected melanoma.	7 (4)
Exclusion criteria 2C: Serious/uncontrolled medical disorder/active infection that may increase risk associated with study participation, study drug administration, or would impair the ability of the subject to receive protocol therapy.	6 (3)
Exclusion criteria 2D: Subjects with previous malignancies are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is anticipated to be required during study period.	6 (3)
Inclusion criteria 1A: Signed & dated an IRB/IEC approved ICF in accordance with regulatory & institutional guidelines. Must be obtained before performance of any protocol related procedures.	5 (2)
Exclusion criteria 4AIV: AST/ALT >10xULN or T.Bilirbin >5xULN	3 (2)
Inclusion criteria 2B: Histologically confirmed Stage III (unresectable) or Stage IV melanoma.	3 (2)
Inclusion criteria 2F2B: if BRAF V600+: objective evidence of PD post treatment with a BRAF inhibitor / Relapse ≤ 6 months of last dose of BRAF inhibitor for adjuvant treatment for completely resected melanoma.	3 (2)
Exclusion criteria 1D: Subjects melanoma BRAF status unknown	2 (1)
Exclusion criteria 2F: Condition requiring systemic treatment with either corticosteroids/other immunosuppress medication within 14 days of study treatment.	2 (1)
Inclusion criteria 2F2A: BRAF V600+: Objective evidence of PD post treatment with anti-CTLA-4 containing therapy / Relapse ≤ 6 months of last dose of anti-CTLA-4 adjuvant treatment for completely resected melanoma.	2 (1)
Inclusion criteria 2F2C: BRAF V600+: Subjects may have received prior anti-CTLA-4 therapy and a BRAF inhibitor in any sequence or in combination.	2 (1)
Exclusion criteria 1B: Ocular melanoma.	1 (<1)
Exclusion criteria 1C: Subjects whose melanoma is BRAF status unknown.	1 (<1)
Exclusion criteria 2B: Prior systemic melanoma therapy with both dacarbazine and carboplatin and paclitaxel. Prior systemic therapy with one of the treatments is permitted.	1 (<1)
Exclusion criteria 2E: Active autoimmune disease.	1 (<1)
Exclusion criteria 2H: Known drug or alcohol abuse.	1 (<1)
Exclusion criteria 3A: Positive test result for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) / hepatitis B or hepatitis C virus indicating acute or chronic infection.	1(<1)
Exclusion criteria 4AV: Subjects who required infliximab or other immune suppressants including mycophenolic acid for management of drug related toxicities.	1 (<1)
Exclusion criteria 4C: History of Grade ≥ 3 allergy to study drug components.	1 (<1)
Exclusion criteria 5A: Women of child-bearing potential who are pregnant or breastfeeding.	1 (<1)

Inclusion criteria 2F1B: BRAF wildtype: In addition to PD post anti-CTLA-4 treatment, subjects that have received another treatment regimen must have objective evidence of PD during/following at least 1 cycle of treatment for advanced melanoma.	1 (<1)
Inclusion criteria 2I: Prior palliative radiotherapy / Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.	1 (<1)
Inclusion criteria 3B: Women of child-bearing potential must use contraception and avoid pregnancy 23wks after last dose BMS-936558/ (nivolumab). Should use adequate meth to avoid pregnancy 30days after last dose of dacarbazine/carboplatin/paclitaxel.	1 (<1)

Source: IE.xpt

Reviewer comment:
These screen failures are not expected to impact the generalizability of the efficacy or safety analyses of trial CA209037.

In this open-label study, 35 (9%) of the 405 patients who were randomized were not treated with study medication. In the all randomized population, more patients in investigator's choice group did not receive treatment compared to the nivolumab group (25% vs. 1%). Table 9 summarizes the reasons patients were randomized but not treated in the treated ORR population.

Table 9: Treatment Disposition Treated ORR Population

Reason	**Nivolumab N=122 n (%)**	**Investigator's choice N=60 n (%)**	**All N=187 n (%)**
All randomized but not treated	2 (2)	13 (22)	15 (8)
Reasons for not being treated			
Subject withdrew consent	1 (<1)	9 (15)	10 (5)
Subject request to discontinue study treatment	0	3 (5)	3 (2)
Poor/non-compliance	1 (<1)	0	1 (<1)
Subject no longer meets study criteria	0	1 (2)	1 (<1)

Source: ADSL.xpt

Reviewer Comment:
More patients in the investigator's choice arm withdrew consent or requested to discontinue study treatment. This is not unexpected in an open-label trial with standard cytotoxic therapy compared to an investigational agent, and is not expected to affect the interpretation of the efficacy analyses of trial CA209037.

At the time of data cut-off, the proportion of patients still on therapy was higher in the nivolumab group (42%) compared to the investigator's choice group (8%). Progression of disease was the most common reason for treatment discontinuation in both groups (58% and 91% in the nivolumab and investigator's choice group, respectively). Five percent of patients in the nivolumab group and 6% in the investigator's choice group discontinued therapy for study drug toxicity. Eight percent of patients in the investigator's choice and 3% of patients in the nivolumab group either requested to

discontinue treatment or withdrew study consent. Death was the reason for treatment discontinuation for 2% of patients in the nivolumab and none in the investigator's choice group. Table 10 summarizes the summary of treatment discontinuation for subjects in the treated ORR population.

Table 10: Summary of Subject Disposition by Treatment Discontinuation

	Nivolumab N=120 n (%)	Investigator's choice N=47 n (%)	All N=167 n (%)
Ongoing	51 (42)	4 (8)	55 (33)
Treatment discontinuation	69 (58)	43 (91)	112 (67)
Progressive disease	56 (47)	30 (64)	86 (51)
Study drug toxicity	6 (5)	3 (6)	9 (5)
Subject request to discontinue study treatment	3 (2)	2 (4)	5 (3)
Subject withdrew consent	1 (1)	2 (4)	3 (2)
Adverse event unrelated to study drug[a]	1 (1)	2 (4)	3 (2)
Death[b]	2 (2)	0	2 (1)
Maximum clinical benefit[c]	0	2 (4)	2 (1)
Other [d]	0	1 (2)	1 (1)
Poor/non-compliance	1 (1)	0	1 (1)

Source: DS.xpt, ADSL.xpt, CRF
[a] Nivolumab group: pneumonia (CA209037-2-37032); investigator's choice group: shortness of breath requiring hospitalization (CA209037-10-37065); fatigue (CA209037-77-37201)
[b] Nivolumab group: sudden death due to probable PE as per investigator on CFR, autopsy report states pneumonia (CA209037-30-37309); death due to disease (CA209037-52-37059)
[c] Defined in CRF as "the investigator has determined that the subject will not benefit from further study treatment"
[d] Investigator's choice: Subject developed hypotension and had a decline in performance status (CA209037-86-37198)

The majority of patients in both groups continued on study at the time of data cut-off. The most common reason for study discontinuation in both groups was death, which was attributed to disease progression in all except one patient in the nivolumab group. Table 11 summarizes the reasons for study discontinuation in the treated ORR population.

Table 11: Summary of Subject Disposition by Study Discontinuation

	Nivolumab N=120 n (%)	Investigator's choice N=47 n (%)	All N=167 n (%)
Ongoing	84 (70)	28 (60)	112 (67)
Study discontinuation	36 (30)	19 (40)	55 (33)
Death[a]	25 (21)	13 (28)	38 (23)
Other[b]	7 (6)	3 (6)	10 (6)
Lost to follow-up	3 (2)	1 (2)	4 (2)
Subject withdrew consent	1 (1)	2 (4)	3 (2)

Source: DS.xpt, ADSL.xpt, CRF
[a] Cause of death listed as disease for all patients except CA209037-30-37309 in the nivolumab group which is listed as sudden death from PE

[b] According to information request (IR) response received from BMS on 11/20/14, the reasons for study discontinuation listed as "other" were taken from the study discontinuation CRF form. For one of each of the patients in the nivolumab and investigator's choice group the reason was that the patient care was transferred to another hospital. For the eight cases when this form was not filled out, BMS used the reason for therapy discontinuation as the reason for study discontinuation which was disease progression for all patients.

6.1.4 Analysis of Primary Endpoint(s)

Please refer to the FDA Statistical BLA Review conducted by Sirisha Mushti, Ph.D., Statistical Reviewer, Division of Biometrics V, Office of Biostatistics, for additional details of the FDA analyses of the primary endpoint for this application.

Overall Response Rate and Duration of Response by BICR

The co-primary endpoints of trial CA209037 are ORR (complete and partial responses) as assessed by BICR per RECIST v1.1 and OS of patient treated with nivolumab compared to investigator's choice chemotherapy. The primary endpoint for the interim analysis presented for this BLA, as agreed upon by FDA, is a single-arm analysis of the BICR-assessed ORR in the first 120 randomized patients treated with nivolumab with at least 6 months of follow-up (treated ORR population). The results of the investigator's choice group are being presented in a non-comparative fashion to demonstrate the effect of chemotherapy for this patient population. The duration of response (DOR) was an additional outcome measure of efficacy to support the ORR. The BICR was a retrospective review conducted by [redacted] (b) (4) as per the review charter version 1.0 dated December 9, 2013.

The results from the treated ORR population showed that the ORR in the nivolumab group was 31.7% (95% CI: 23.5, 40.8). Thirty-eight patients had an objective response; four patients (3.3%) had a complete response (CR) and the other 34 (28.3%) had a partial response (PR).

The median DOR was not reached (range 1.4 to 10+ months). The Applicant reported that 95% of the responses were ongoing at the time of data cutoff; however, according to this reviewer's analysis, responses were ongoing in 87% of the patients who responded. This analysis is based on the following: of the 38 patients with an objective response, one patient had progression of disease at 3.8 months, one died following a response duration of 4.4 months, and three were censored by the BICR for receiving subsequent therapy following response durations of 1.4, 1.5, and 5.6 months. The duration of response among the remaining 33 patients ranges from 2.6+ to 10+ months, which includes 13 patients with ongoing responses of 6 months or longer.

The ORR in the treated ORR population in the investigator's choice group was10.6% (95% CI: 3.5, 23.1). Of the five patients with an objective response, all had a PR and received the carboplatin and paclitaxel chemotherapy regimen. The median duration of response was 3.6 months (range 1.3+, 3.5).

Table 12 summarizes the ORR for patients treated with nivolumab and investigator's choice chemotherapy in the treated ORR population, Table 13 lists the duration of response for the individual patients who achieved an objective response as assessed by the BICR, and Figure 1 plots the duration of response and time to response for each responder in the nivolumab group.

Table 12: Response Rate and Duration of Response based on BICR per RECIST 1.1 in Treated ORR Population

	Nivolumab N=120	**Investigator's choice N=47**
ORR, n (%)	38 (31.7)	5 (10.6)
95% CI	(23.5, 40.8)	(3.5, 23.1)
CR, n (%) PR, n (%)	4 (3.3) 34 (28.3)	0 5 (10.6)
Median Duration of Response, months (range)	Not reached (1.4, 10+)	3.6 (1.3+, 3.5)
Response ongoing (%)	87[*]	40[**]

Source: Adapted from FDA Statistical Review, CRFs
CR=Complete Response, PR=Partial Response
[*] Out of 38 patients with an overall response of CR or PR; one had progressive disease (PD), one died of disease, three received subsequent therapy, and 33 had ongoing responses at the time of data cut-off
[**] Out of the five patients with an overall response of PR; one had PD, one received subsequent therapy, one withdrew consent, and two had ongoing responses at the time of data cut-off

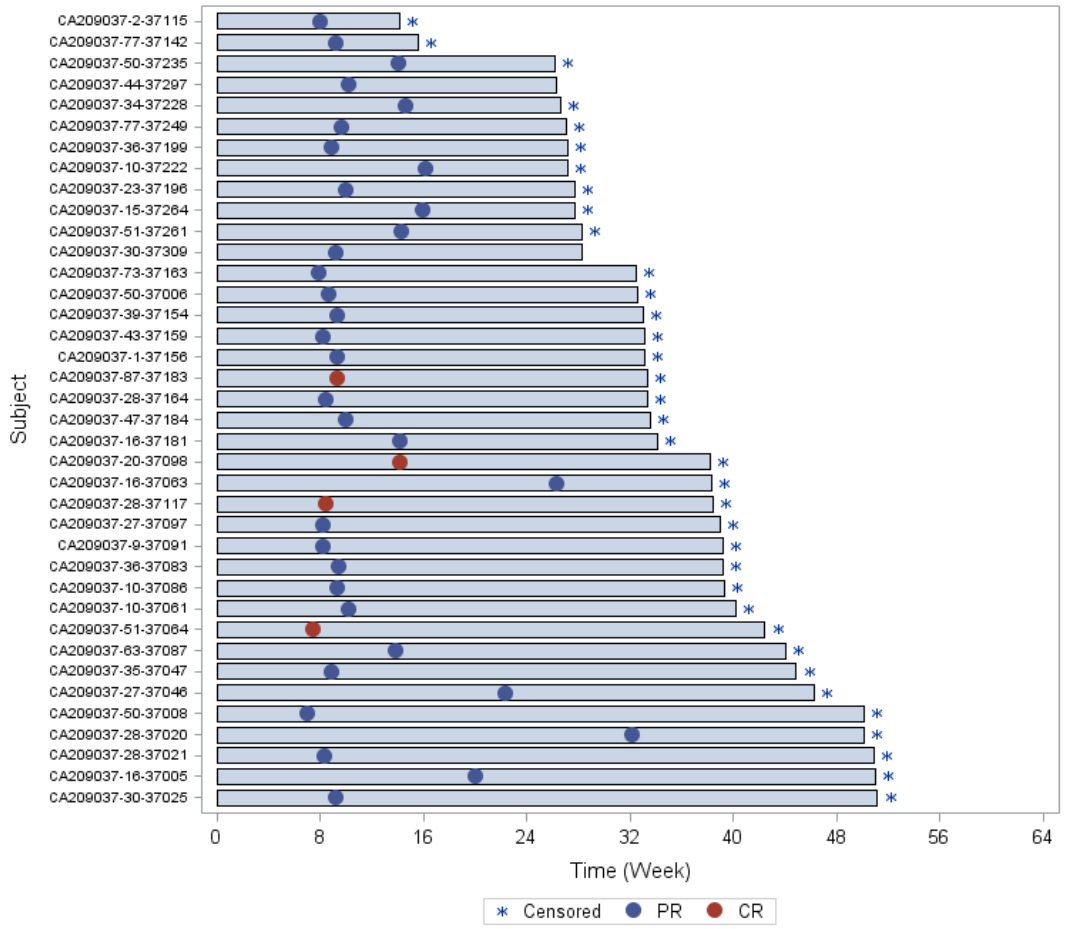
Table 13: Response Duration by BICR per RECIST 1.1 in Treated ORR Population

Patient ID	**Duration of response in months**
CA209037-2-37115[a]	1.4
CA209037-77-37142[a]	1.5
CA209037-44-37297[b]	3.8
CA209037-30-37309[c]	4.4
CA209037-50-37006[a]	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+
CA209037-16-37181[d]	4.6+
CA209037-47-37184	5.4+

Patient ID	Duration of response in months
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+
CA209037-43-37159[d]	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+
CA209037-35-37047[d]	8.3+
CA209037-30-37025	9.7+
CA209037-28-37021	9.8+
CA209037-50-37008	10+

Source: Adapted from FDA Statistical Review, CRFs
+ indicates subjects with an ongoing response at the time of data cutoff
[a] Patient received subsequent therapy and was censored by BICR at time of therapy
[b] Patient had disease progression
[c] Patient died
[d] 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]

Figure 1: Plot of Time to Response and Duration of Response in Treated ORR Population



Source: FDA Statistical Review

Reviewer Comments:

1. *The ORR of 32% with a median duration of response that was not reached but duration that ranged from 1.4 to 10+ months in a refractory population in this interim analysis is used as a surrogate endpoint that is reasonably likely to predict clinical benefit and appears to provide meaningful advantage over available therapy. Responses were ongoing in 87% of the patients in the nivolumab group at the time of data cutoff and suggest the potential for a durable response in this refractory population with limited available treatment options.*
2. *Figure 1 shows that most patients responded by the first disease assessment at 9 weeks; four of the 38 patients achieved a response after 16 weeks of nivolumab.*
3. *A total of 83 (50%) patients [62 (52%) in the nivolumab group] required adjudication by a third radiologist in the BICR.*

4. *The discrepancy in the Applicant's analysis of ongoing responders and this reviewer's analysis resides in the definition of ongoing responders. The Applicant defined ongoing responders as any patient who did not have an event of death of progressive disease by BICR at the time of data cutoff. The Applicant also censored the three patients who received subsequent therapy and considered 33 of 35 patients as having ongoing responses. This reviewer did not agree with censoring patients in this descriptive analysis and counted the three patients who had PD as assessed by the investigator and went on to receive subsequent therapy as non-responders. This reviewer's analysis identified 33 out of 38 patients as ongoing responders.*
5. *Objective responses could not be determined in 12 (10%) patients in the nivolumab group and 11 (23%) patients in the investigator's choice group.*
    a. *Per the Applicant reasons in the nivolumab group include:*
        i. *Clinical progression prior to first tumor assessment, N=7 (CA209037-2-37069, CA209037-14-37211, CA209037-16-37273, CA209037-29-37149, CA209037-50-37189, CA209037-52-37059, CA209037-63-3727)*
        ii. *Censoring due to patient receiving additional anti-cancer therapy prior to the first scan, N=5*
            1. *Data received from Applicant on 11/20/14 in response to information request (IR) stated that the reasons for censoring were as follows: [CA209037-2-37016 (clinical progression and radiotherapy), CA209037-13-37161 (AE of fistulating tumor mass and surgery), CA209037-27-37252 (excision of skin lesions), CA209037-51-37023 (radiographic progression and radiotherapy), CA209037-62-37153 (clinical progression and radiotherapy)]*
    b. *Per the Applicant reasons in the investigator's choice group include:*
        i. *Clinical progression prior to first tumor assessment, N=3 (CA209037-10-37065, CA209037-38-37051, CA209037-67-37077)*
        ii. *Censoring due to patient receiving additional anti-cancer therapy prior to the first scan, N=7*
            1. *Data received from Applicant on 11/20/14 in response to IR stated that the reasons for censoring were as follows: [CA209037-10-37168 (radiographic progression and surgery), CA209037-38-37185 (radiographic progression and chemotherapy), CA209037-51-37011 (radiographic progression and chemotherapy), CA209037-62-37224 (patient requested discontinuation of therapy for non-toxicity related concerns and began alternative chemotherapy), CA209037-42-37212 (clinical progression and chemotherapy), CA209037-50-37262, CA209037-86-37198 (clinical progression and radiotherapy)]*
        iii. *Withdrawal of consent, N=1 (CA209037-34-37162)*

c. *This is not likely to impact the interpretation of the efficacy of nivolumab in a single arm analysis.*

Overall Response and Duration of Response by Investigator in Trial CA209003

The overall response and duration of response from melanoma patients treated on trial CA209003 were evaluated as supportive evidence for efficacy. Of the 107 patients with refractory melanoma treated on this study, 87 received 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). Based on the datasets provided to FDA with a cutoff date of March 2013, the ORR in these 87 patients was 33.3% (95% CI: 23.6, 44.3), the median DOR was 22.9 months (95% CI: 12.9, NR) with a range of 4.2 to 26.6+ months, and approximately 47% of the patients had ongoing responses at the time of data-cutoff. (The accuracy of the percentage of patients with ongoing responses is questionable given the data collection during this trial; see reviewer's comments below for further discussion). A summary of ORR and DOR for patients on trial CA209003 is presented in in Table 14. Table 15 lists the duration of response for the individual patients who achieved an objective response as assessed by the investigator.

Table 14: ORR and DOR in Patients with Advanced Melanoma on Trial CA209003

	Nivolumab 0.1mg/kg N=17	**Nivolumab 0.3 mg/kg N=18**	**Nivolumab 1 mg/kg N=35**	**Nivolumab 3 mg/kg N=17**	**Nivolumab All ≤ 3 mg/kg N=87**
ORR, n (%)	6 (35.3)	5 (27.8)	11 (31.4)	7 (41.2)	29 (33.3)
95%CI	(14.2, 61.7)	(9.7, 53.5)	(16.9, 49.3)	(18.4, 67.1)	(23.6, 44.3)
Median Duration of Response, months (95% CI)	NR (5.55, NR)	NR (4.24, NR)	23.95 (7.46, NR)	17.46 (9.3, NR)	22.9 (12.9, NR)
Response ongoing (%)* (see reviewer comment below)	33	60	54	29	77

Source: Adapted from FDA Statistical Review based on analysis using datasets provided to FDA with a cutoff date of March 2013; Applicant Response to 11/13/14 and 12/2/14 FDA Information Request

Table 15: Response Duration by Investigator per RECIST 1.0 in Trial CA209003

Patient ID	**Duration of Response (months)[a]**	**Duration of Response (months)[b]**	**Reason Off Therapy/Study**
Nivolumab 0.1 mg/kg			
CA209003-1-111	5.6	5.6	PD
CA209003-10-116	5.6	5.6	PD

CA209003-1-217	7.9	7.9	PD
CA209003-10-103	11.2+	11.2	PD
CA209003-10-130	10.2+	10.2+	AE
CA209003-5-140	11.1+	18.4+	N/A
Nivolumab 0.3 mg/kg			
CA209003-1-207	4.2	4.2	other
CA209003-7-143	15+	20.7	completed max cycles
CA209003-5-210	10.2+	15.7+	N/A
CA209003-7-139	14.8+	20.5+	completed max cycles
CA209003-7-129	15.2+	21.4+	completed max cycles
Nivolumab 1 mg/kg			
CA209003-6-136	7.5	7.5	AE
CA209003-3-138	7.5	16.7	CR
CA209003-4-1315	22.9	22.9	PD
CA209003-11-1324	23.2+	23.2	withdrew consent
CA209003-7-1309	24	24	PD
CA209003-1-215	10+	15.6+	N/A
CA209003-3-127	17.0+	17+	AE
CA209003-10-1319	18.4+	18.4+	completed max cycles
CA209003-3-101	19+	19+	AE
CA209003-12-148	14.8+	19.4+	N/A
CA209003-3-1303	24.9+	24.9+	completed max cycles
Nivolumab 3 mg/kg			
CA209003-10-2314	9.2+	9.2	other
CA209003-5-2309	9.3	9.3	PD
CA209003-3-2304	11.1	11.1	CR
CA209003-5-2313	12.9	12.9	PD
CA209003-1-2316	22.0	22	other (completed max cycles, inv decision)
CA209003-1-2315	24.5+	24.5+	CR
CA209003-7-2312	26.6+	26.6+	completed max cycles

Source: Adapted from FDA Statistical Reviewer; ADEF.xpt; BMS response to FDA IR dated 12/2/14
Abbreviations: PD= progressive disease; AE=adverse event; CR=complete response; max=maximum; inv=investigator; N/A= not applicable, patient remained on therapy at time of data cutoff
+ indicates subjects with an ongoing response at the time of data cutoff
[a] Data based on data cutoff of March 2013
[b] Data based on data cutoff of September 2013

Reviewer Comments:

1. *The similar ORR and longer duration of follow up with median sustained responses of 23 months in this study provides supportive evidence of efficacy of nivolumab in patients with refractory melanoma. Patients in this study were naïve*

to ipilimumab but of the 107 patients with refractory melanoma, all but one were previously treated with chemotherapy and 62% received two or more prior regimens, representing a heavily pre-treated patient population.

2. *Per the Applicant, the duration of response in this trial was based on documented radiographic progression by the investigator and did not take clinical progression into account. Also, data on subsequent therapy was not collected during the course of this study.*
3. *The Applicant stated that the ORR in these 87 patients was 34.5% (95% CI: 24.6, 45.4), with a median DOR of 22.9 months (95% CI: 16.6, NR), a range of 3.9+ to 26.5+ months, and with 57% (17/30) of the patients with ongoing responses at the time of data-cutoff. This information was based on the updated CSR with a data cutoff of September 2013. Datasets provided to FDA were based on an earlier cutoff date of March 2013. The following discrepancies resulted between this reviewer's and the Applicant's review:*
    a. *FDA review identified only 29 responders. The Applicant stated that one additional patient had responded by the September 2013 cutoff date.*
    b. *Duration of responses differed between the two analyses as noted in the table.*
4. *The Applicant stated that 57% of patients had ongoing responses at the time of final data cutoff. This reviewer does not agree with this statement and concluded that only approximately 47% of the patients should be considered ongoing responders; however, even this percentage is uncertain as there are limitations in interpreting the data that was collected from the trial (see next comment). For the ongoing responder analysis, this reviewer does not agree that patients CA209003-10-103, A209003-11-1324, and CA209003-10-2314 should be considered as ongoing responders based on the following clarification received from the Applicant in response to an FDA IR of 12/2/14:*
    a. *Per the Applicant: "Patient CA209003-10-103 had an objective response of partial response (PR) on 06-Jun-2011 and continued to respond and was censored on the last tumor assessment date, 11-May-2012. The patient discontinued the study drug due to an adverse event (last dose date was 31-May-2012) and was followed until 03-Jan-2013, when the patient discontinued the study due to disease progression per investigator assessment without documented lesion measurements."*
        i. *This reviewer does not agree that this patient should be counted as an ongoing responder given investigator-assessed PD in Jan 2013.*
    b. *Per the Applicant: "Patient CA209003-11-1324 had an objective response of PR on 12-Jun-2010 and continued to respond and was censored on the last tumor assessment date, 17-May-2012. The patient withdrew consent on 10-Jan-2012 for study drug discontinuation and later for study discontinuation on 11-Jul-2012. No additional information is available regarding the reason for withdrawal of consent for study drug discontinuation or study discontinuation by this patient."*

   i. *This reviewer does not agree that this patient should be counted as an ongoing responder as the patient withdrew consent in Jan 2012 and no further information is available after that time.*

c. *Per the Applicant: "Patient CA209003-10-2314 had an objective response of PR on 10-Mar-2010 and continued to respond and was censored on the last tumor assessment date, 15-Dec-2010. The verbatim text associated with 'other' as reason for study drug discontinuation is "MD discretion". No other information is available."*
   i. *This reviewer does not agree that this patient should be counted as an ongoing responder as there is no further information available after Dec 2010.*

5. *The data for DOR from trial CA209003 is reliable as the censoring rules were applied appropriately at the last scan prior to PD or withdrawal of consent. However; the percentage of patients with an ongoing response is less reliable given that clinical progression was not considered, subsequent therapy was not captured on this study, patients with clinical progression were counted as ongoing responders by the Applicant, and it is possible that patients went on to receive other therapy without radiographic documentation of disease. For this reason, the percentages for ongoing responders should be interpreted with caution given the limitations in the data. This does not affect the overall efficacy assessment of nivolumab as the ORR and DOR are the primary measures of efficacy assessed for this BLA.*

6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints of trial CA209037 include an evaluation of PFS of the two treatment groups and the impact of PD-L1 expression as a predictive biomarker for ORR and OS. The prespecified number of events for the analysis of PFS had not occurred at the time of data cutoff and the analyses provided by the Applicant and presented in this review are non-comparative and descriptive only. The analysis of tumor PD-L1 expression is also preliminary as it is based on a verified but not validated assay. The Applicant stated that the final results of the secondary endpoints will be provided with the final trial results.

Progression-free Survival

As summarized in Table 16, in the descriptive analysis of PFS as assessed by BICR in the ORR population, the median PFS was 4.7 months (95% CI: 2.3, 6.5) in the nivolumab group and 4.2 months (95% CI: 2.1, 6.3) in the investigator's choice group. Figure 2 shows the Kaplan-Meier plot for PFS as assessed by the BICR.

An additional analysis was performed for PFS as assessed by BICR and the investigator for the treated ORR population (nivolumab, N=120; investigator's choice, N=47) with similar results as seen in Table 17.

Table 16: Descriptive analysis of Progression Free Survival by BICR in the ORR Population

	Nivolumab N=122	Investigator's Choice N=60
Events N (%)	71 (58.2)	26 (43.3)
Median (95% CI)	4.7 (2.3, 6.5)	4.2 (2.1, 6.3)
Unadjusted HR	0.74 (0.47, 1.16)	
Nominal p-value*	0.18	

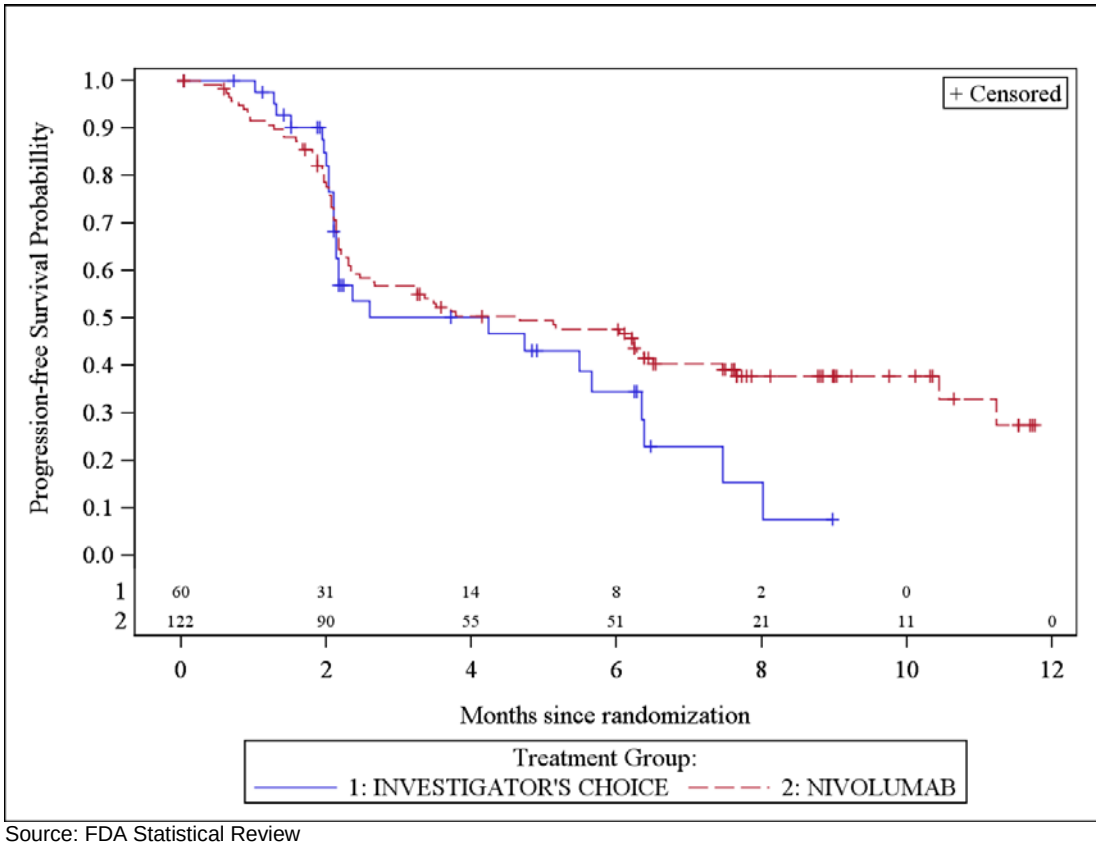
Source: Adapted from FDA Statistical Review
HR=hazard ratio
*p-value: two-sided, unstratified logrank test

Table 17: Descriptive analysis of Progression Free Survival by BICR and Investigator treated in the Treated ORR Population

	PFS by BICR		PFS by Investigator	
	Nivolumab N=120	Investigator's choice N=47	Nivolumab N=120	Investigator's choice N=47
Events N (%)	70 (58.3)	26 (55.3)	71 (59.2)	33 (70.2)
Median (95% CI)	4.7 (2.3, 6.5)	4.2 (2.1, 6.3)	3.6 (2.3, 6.5)	2.2 (2.1, 4.2)
Unadjusted HR	0.73 (0.46, 1.16)		0.62 (0.41, 0.94)	
Nominal p-value*	0.1773		0.0212	

Source: Adapted from FDA Statistical Review
HR=hazard ratio
*p-value: two-sided, unstratified logrank test

Figure 2: Kaplan-Meier Curve of Progression Free Survival by BICR in the ORR Population



Source: FDA Statistical Review

Reviewer comments:

1. *The analyses presented in Table 16, Table 17, and Figure 2 performed by the FDA Statistical Reviewer were performed using unstratified logrank tests given the small number of events and the interim nature of the analysis. This resulted in slightly different results from those presented by the Applicant in the clinical study report (CSR) using the stratified analysis that was agreed-upon by FDA for the final analysis of PFS. The result for the median PFS was similar; however, the resulting HRs and p-values were different. Given the very preliminary, non-comparative nature of these analyses, these results should be interpreted with caution regardless of the analysis.*
2. *The median PFS by investigator was slightly lower but at 3.6, but confidence intervals were overlapping. The BICR assessment is considered the primary method of analysis in this open-label trial.*

Impact of PD-L1 Tumor Expression on ORR

All patients had tumor tissue that was collected prior to randomization and after any previous therapy for determination of PD-L1 status that was used for stratification.

Patients were designated as PD-L1 positive, defined as ≥5% tumor cell membrane expression of PD-L1 by verified BMS immunohistochemistry assay, or negative/indeterminate. The Applicant states that results of PD-L1 expression using a validated assay will be analyzed at a later date and submitted with the formal OS analyses. The ORR rate was higher in patients who were PD-L1 positive [43.6% (95% CI: 30.3, 57.7)]; however, responses were also see in patients who were PD-L1 negative or indeterminate [20.3% (95% CI: 11.3, 33.6). Also see Figure 3 for effect of PD-L1 expression.

Reviewer Comment:
The true impact of tumor PD-L1 expression in this preliminary analysis is unclear as the statistical design of the trial was not adequate to answer this question and the assay used per BMS was a verified, though not validated assay. A premarketing application (PMA) has not been submitted for use of the BMS assay as a companion diagnostic for selection of melanoma patients prior to treatment with nivolumab.

6.1.6 Subpopulations

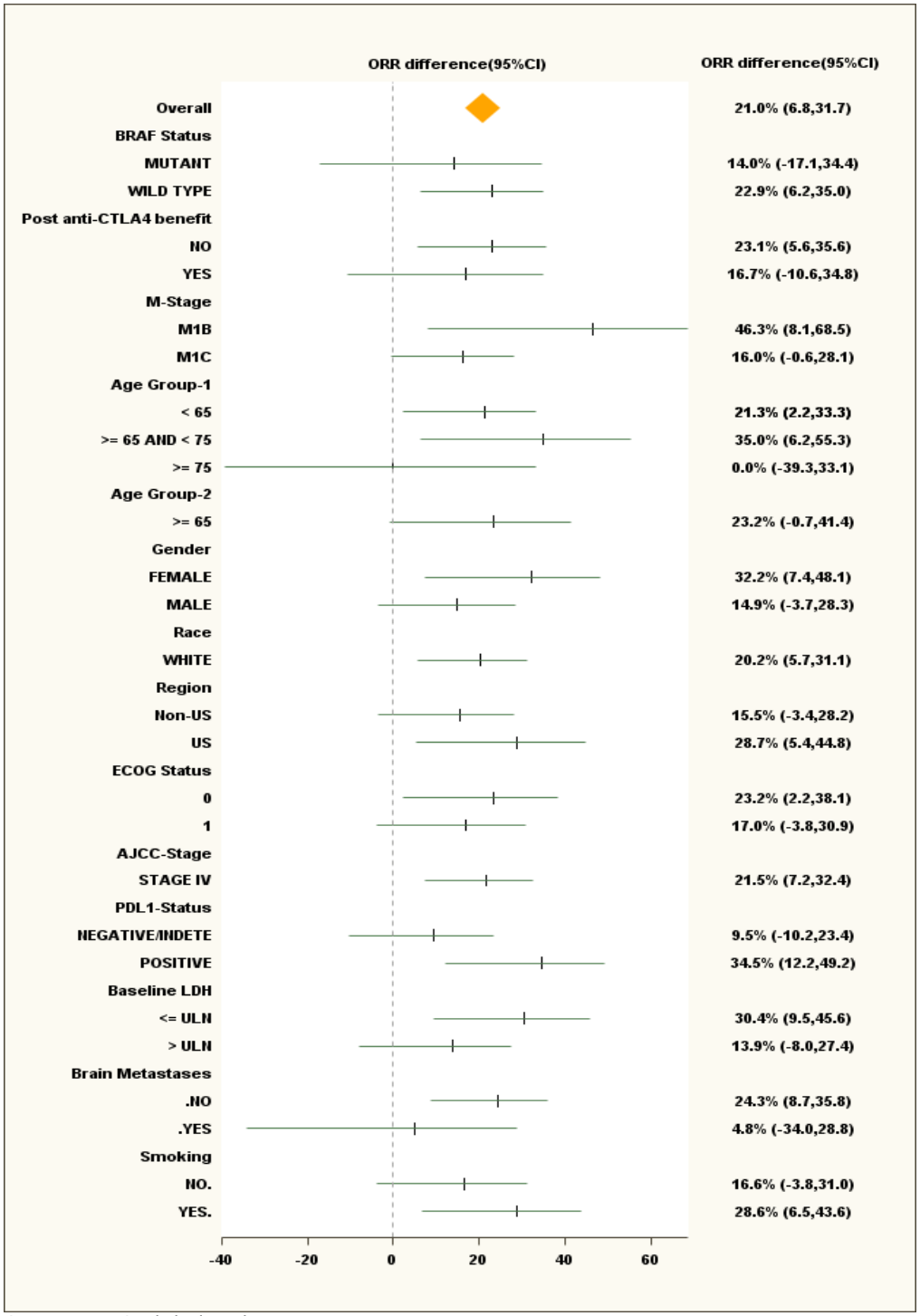
Exploratory subgroup analyses of response rate were evaluated by Dr. Sirisha Mushti, FDA Statistical Reviewer. The subgroups that were analyzed were demographic characteristics including age, gender, and race, and disease characteristics including stage, history of brain metastases, baseline LDH, ECOG performance status, BRAF status, PD-L1 status, and prior anti-CTLA-4 benefit. Only subgroups with sufficient sample size are reported. Table 18 summarizes the subgroup analyses in the treated ORR population and Figure 3 shows the forest plot for the unweighted differences in ORR between treatment groups. Overall, the results of the subgroup analyses were consistent with those of the primary analysis of the treated ORR population.

Table 18: Subgroup Analysis of ORR by Baseline Demographics by BICR per RECIST v.1.1

Subgroup Variable		Nivolumab		Investigator's Choice		Unweighted ORR Difference (%) (95% CI)
		N=120 (n)	ORR (%) (95% CI)	N=47 (n)	ORR (%) (95% CI)	
Overall		38/120	31.7 (23.5, 40.8)	5/47	10.6 (3.5, 23.1)	21.0 (6.8,31.7)
BRAF Status	Mutant	6/26	23.1 (9.0, 43.6)	1/11	9.1 (0.2, 41.3)	14.0 (-17.1,34.4)
	Wild Type	32/94	34.0 (24.6, 44.5)	4/36	11.1 (3.1, 26.1)	22.9 (6.2,35.0)
Prior Anti-CTLA-4 benefit	No	26/80	32.5 (22.4, 43.9)	3/32	9.4 (2.0, 25.0)	23.1 (5.6,35.6)
	Yes	12/40	30.0 (16.6, 46.5)	2/15	13.3 (1.7, 40.5)	16.7 (-10.6,34.8)
M stage at study entry	M0	1/5	20.0 (0.5, 71.6)			
	M1a	3/8	37.5 (8.5, 75.5)			
	M1b	9/16	56.3 (29.9, 80.2)	1/10	10.0 (0.3, 44.5)	46.3 (8.1,68.5)
	M1c	25/91	27.5 (18.6, 37.8)	4/35	11.4 (3.2, 26.7)	16.0 (-0.6,28.1)
Age group 1	< 65	24/82	29.3 (19.7, 40.4)	2/25	8.0 (1.0, 26.0)	21.3 (2.2,33.3)
	>= 65 And < 75	10/24	41.7 (22.1, 63.4)	1/15	6.7 (0.2, 31.9)	35.0 (6.2,55.3)
	>= 75	4/14	28.6 (8.4, 58.1)	2/7	28.6 (3.7, 71.0)	
Age group 2	< 65	24/82	29.3 (19.7, 40.4)	2/25	8.0 (1.0, 26.0)	21.3 (2.2,33.3)
	>= 65	14/38	36.8 (21.8, 54.0)	3/22	13.6 (2.9, 34.9)	23.2 (-0.7,41.4)
Gender	Female	16/42	38.1 (23.6, 54.4)	1/17	5.9 (0.1, 28.7)	32.2 (7.4,48.1)
	Male	22/78	28.2 (18.6, 39.5)	4/30	13.3 (3.8, 30.7)	14.9 (-3.7,28.3)
Race	Asian	1/2	50.0 (1.3, 98.7)			
	White	37/118	31.4 (23.1, 40.5)	5/45	11.1 (3.7, 24.1)	20.2 (5.7,31.1)
Region	Non-US	16/68	23.5 (14.1, 35.4)	2/25	8.0 (1.0, 26.0)	15.5 (-3.4,28.2)
	Us	22/52	42.3 (28.7, 56.8)	3/22	13.6 (2.9, 34.9)	28.7 (5.4,44.8)
ECOG PS	0	27/70	38.6 (27.2, 51.0)	4/26	15.4 (4.4, 34.9)	23.2 (2.2,38.1)
	1	11/50	22.0 (11.5, 36.0)	1/20	5.0 (0.1, 24.9)	17.0 (-3.8,30.9)
Brain Metastases	No	34/99	34.3 (25.1, 44.6)	4/40	10.0 (2.8, 23.7)	24.3 (8.7,35.8)
	Yes	4/21	19.0 (5.4, 41.9)	1/7	14.3 (0.4, 57.9)	4.8 (-34.0,28.8)
AJCC Stage at study entry	Stage III	1/5	20.0 (0.5, 71.6)			
	Stage IV	37/115	32.2 (23.8, 41.5)	5/47	10.6 (3.5, 23.1)	21.5 (7.2,32.4)
PD L1 Status	Negative/Indeterminate	14/65	21.5 (12.3, 33.5)	3/25	12.0 (2.5, 31.2)	9.5 (-10.2,23.4)
	Positive	24/55	43.6 (30.3, 57.7)	2/22	9.1 (1.1, 29.2)	34.5 (12.2,49.2)
Baseline LDH	<= ULN	22/53	41.5 (28.1, 55.9)	3/27	11.1 (2.4, 29.2)	30.4 (9.5,45.6)
	> ULN	16/67	23.9 (14.3, 35.9)	2/20	10.0 (1.2, 31.7)	13.9 (-8.0,27.4)

Source: Adapted from FDA Statistical Review

Figure 3: Forest Plot of ORR by Baseline Demographics and Characteristics by BICR per RECIST v. 1.1



Source: FDA Statistical Review

Reviewer Comment:

The treatment effect of nivolumab as assessed by ORR was consistent across all demographic and disease-related characteristics evaluated; however, the numbers of patients in these exploratory interim comparative analyses were small and results should be interpreted with caution.

6.1.7 Other Endpoints to Support Efficacy

Overall Response Rate and Duration of Response by Investigator

The investigator-assessed ORR in the treated ORR population was 25.8% (95% CI: 18.3, 34.6) in the nivolumab group and 10.6% (95% CI: 3.5, 23.1) in the investigator's choice group. According to FDA statistical review, there was 75.4% concordance between the BICR and the investigator assessments for ORR in the nivolumab treatment arm and 81.7% in the investigator's choice arm. Data corresponding to investigator-assessed DOR was not provided.

Reviewer Comment:
Per the Applicant, the discrepancies between the BICR and investigator-assessed response included the following:

- *Responders per BICR, non-responders per investigator, N=13*
- *Complete responders per BICR, partial responders per investigator, N=3*
- *Non-responders per BICR, responder per investigator, N=6*
- *Partial responder per BICR, complete responder by investigator, N=1*

Descriptive Analysis of Overall Survival

Descriptive, non-comparative analyses of overall survival (OS) for the ORR population and all randomized subjects population are presented in Table 19. The median OS was not reached in the nivolumab group (95% CI: 11.5 months, N.A.) and was 11.8 months (95% CI: 7.8, N.A.) in the investigator's choice group for both populations. Figure 4 shows the Kaplan-Meier curve of OS for the ORR population.

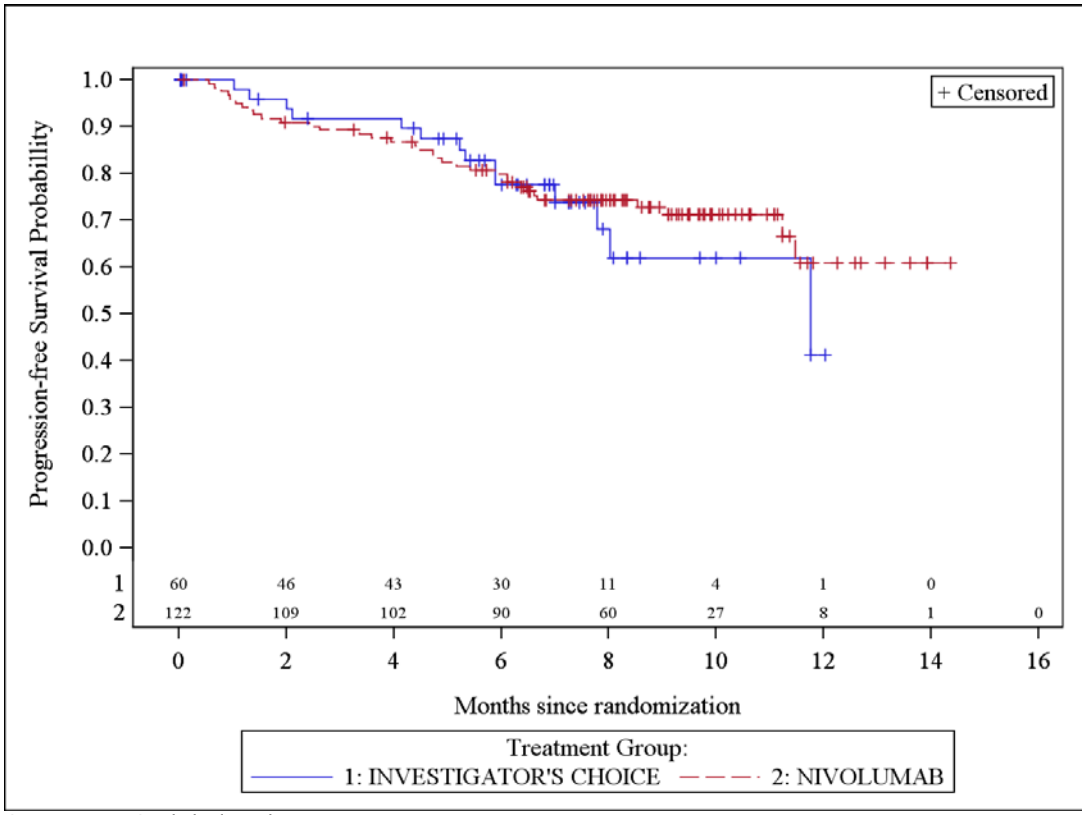
Table 19: Overall Survival in Nivolumab and Investigator's Choice Group in the ORR Population

	Nivolumab n=122	**Investigator's choice n=60**	**Nivolumab N=272**	**Investigator's choice N=133**
Events N (%)	34 (27.9)	14 (23.3)	69 (25.4)	25 (18.8)
Median (95% CI)	NR (11.5, NR)	11.8 (7.8, NR)	NR (11.5, NR)	11.8 (7.8, NR)
HR	0.86 (0.46,1.62)		1.02 (0.64, 1.61)	

Nominal p-value *	0.6478	0.947

Source: FDA Statistical Review
HR=hazard ratio
*p-value: two-sided, unstratified logrank test

Figure 4: Kaplan-Meier Curve of Overall Survival for ORR Population



Source: FDA Statistical Review

Reviewer Comment:
The OS analysis presented in Table 19 and Figure 4 performed by the FDA Statistical Reviewer was completed using an unstratified logrank test given the small number of events and the interim nature of the analysis. This resulted in slightly different results from those presented by the Applicant in the CSR using the stratified analysis that was agreed-upon by FDA for the final analysis of OS. The result for the median OS was similar; however, the resulting HR and p-value were different. Given the very preliminary, non-comparative nature of this analysis, these values should be interpreted with caution regardless of the analysis.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analyses of the exposure-efficacy relationship was performed by Hongshan Li, Ph.D., FDA Pharmacology Reviewer, please see FDA Pharmacology Review for further

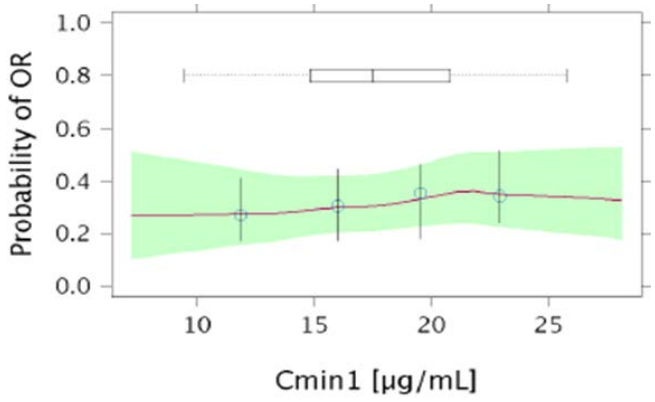
details. In summary, there did not appear to be an exposure-efficacy relationship for the ORR across the dose range of 0.1-10 mg/kg of nivolumab every 2 weeks (Q2W) for the proposed indication based on the clinical efficacy data currently available. Table 20 summarizes the ORR across varying doses of nivolumab for patients with melanoma in trial CA209003 and Figure 5 shows the flat exposure-response relationship that supports the 3mg/kg Q2W dose of nivolumab for the proposed indication.

Table 20: ORR of Melanoma Patients Treated in Trial CA209003

	Nivolumab 0.1 mg/kg N=17	Nivolumab 0.3 mg/kg N=18	Nivolumab 1 mg/kg N=35	Nivolumab 3 mg/kg N=17	Nivolumab 10 mg/kg N=20	Nivolumab All doses N=107
ORR (95% CI)	35.3 (14.2, 61.7)	27.8 (9.7, 53.5)	31.4 (16.9, 49.3)	41.2 (18.4, 67.1)	20 (5.7, 43.7)	30.8 (22.3, 40.5)

Source: Tables 7.2.1-1, 7.3.1-1 and 7.4.1-1 of MDX1106-03 CSR
Source: Adapted from FDA Pharmacology Review

Figure 5: Exposure-Response for the Trough Concentration of the First Dose (C_{min1}) versus Objective Response Rate for 3 mg/kg Q2W of Study CA209037



Red line is the lowest smooth curve of the predicted probability and the light green area is the 95% CI. Open circles are observed ORR for each C_{min1} quartile plotted at the median of the quartile with the vertical bar as the 90% CI. The horizontal boxplot shows the median, interquartile range, and 5th/95th percentiles of C_{min1}.

Source: Figure 5.2.2-1 of the Population Pharmacokinetic and Exposure-Response Report.
Source: Adapted from FDA Pharmacology Review

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Patients Treated Beyond RECIST v1.1 Progression in Trial CA209037

In an exploratory analysis examining the time to onset of the treatment effect patients who were treated beyond investigator-assessed RECIST v1.1-defined progressive

disease on Trial CA209037 were reviewed. Patients were allowed to remain on study provided they were deriving investigator-assessed clinical benefit and were tolerating the study drug (see Section 5.3 for further details). The Applicant stated that of the 120 patients in the treated ORR population, 37 had investigator-assessed RECIST v1.1 progressive disease (PD) and continued to receive nivolumab and that 10 of these 37 had a greater than 30% reduction in target lesion tumor burden compared to baseline after RESIST-defined PD as assessed by the investigator. However, four of these patients had a best confirmed overall response rate of PR by the BICR and were included in the responder population and three of the patients had a 30% or greater reduction in tumor burden as assessed by the investigator prior to RECIST-defined progression. Several patients also received subsequent therapy following their investigator-defined progression. Only one patient (CA209037-2-37085) had a BICR-assessed PR following progressive disease. As assessed by the BICR, the patient had progressive disease as a result of a new bone lesion on the first restaging at week 9 and then went on to have a 32% reduction in target lesion measurements at week 39; however, overall tumor burden decrease at this time was <30%. Table 20 summarizes the patients treated beyond investigator-assessed PD.

Table 21: Patients Treated Beyond Investigator-defined RECIST v1.1 PD

Patient ID	INV BOR	BICR BOR	BICR ≥30% in target lesions after PD	INV ≥30% reduction in target lesion response prior to INV PD	Overall status of non-target disease by BICR	Duration of Treatment beyond INV PD (months)	Subsequent Therapy after INV PD during nivolumab treatment
CA209037-2-37085	PD	PD	Yes	No	Decreased	7.5+	None
CA209037-2-37115	SD	PR	No	No	Increased	3.2	XRT
CA209037-9-37126	PD	PD	No	No	Increased	0.7	None
CA209037-23-37196	PD	PR	No	No	N/A	5.5+	None
CA209037-28-37020	PD	PR	No	No	Decreased	10.7+	None
CA209037-40-37013	PR	SD	No	Yes	Increased	2.5+	Surgery
CA209037-50-37006	PD	PR	No	Yes	N/A	6+	Surgery
CA209037-51-37023	PD	NE	No	No	Increased	3.9	XRT
CA209037-77-37079	PD	PD	No	No	Increased	9+	None
CA209037-77-37272	PR	PD	No	Yes	Decreased	4.2+	Surgery

Source: ADRS.xpt, TU.xpt, Applicant Response to 11/3/2014 FDA Information Request

Abbreviations: INV=investigator; BOR=best overall response; PD=progressive disease; SD=stable disease; NE=not evaluable; XRT=radiotherapy
"+" indicates patients with ongoing nivolumab treatment

Reviewer comments:

1. *The blinded analysis of tumor response by BICR as per RECIST v1.1 is the primary endpoint of study CA209037 for this BLA. Only one patient had BICR-assessed >30% decrease in target lesion tumor burden following a RECIST-based progression based on a new lesion. Response based on investigator assessment in an open-label trial is subject to assessment bias.*
2. *In addition, though there is limited experience with using immune-related response criteria (irRC) as an endpoint in clinical trials and objective tumor responses following progressive disease by this criteria is generally reported to be a rare occurrence, the patients treated on trial CA209037 were not treated in accordance with irRC which takes into consideration the measurements of new lesions into the overall tumor burden. The patient described above would not have met this criteria given the status of their overall tumor burden. Several patients who were reported to have a decrease in target lesions by the investigator also had increases in non-target disease which was not measured or taken into consideration in the Applicant's analysis. Several patients also had an investigator-assessed >30% decrease in target lesions prior to the assessment of PD.*

6.1.10 Additional Efficacy Issues/Analyses

Overall Response Rate as a Surrogate Endpoint for Accelerated Approval

The efficacy data that form the basis of the proposed indication consists of ORR in 120 patients treated with nivolumab in an open-label trial at the proposed dose. The issue of whether ORR is a surrogate for true clinical benefit in this patient population is unresolved and confirmation of established clinical benefit with the final analysis of OS in trial CA209037 or demonstration clinically significant PFS in other ongoing studies will be required as discussed in Section 1.4.

The issue of to what degree tumor expression of PD-L1 is a predictive biomarker for activity with nivolumab is also unknown and additional data will be available with the final trial analysis.

7 Review of Safety

Safety Summary

The safety of nivolumab was primarily evaluated in Trial CA209037, a randomized, open-label trial in patients with previously treated unresectable or metastatic melanoma

who had progressed on ipilimumab and if BRAF V600 positive, a BRAF inhibitor. The clinical review of safety focused on 370 treated patients, 268 patients in the nivolumab group treated at a dose of 3 mg/kg intravenously every 2 weeks and 102 patients in the investigator's choice group treated with either dacarbazine (N=45) or carboplatin/paclitaxel therapy (N=57). The safety review was supplemented with an evaluation of 306 patients with melanoma (107 patients) and non-melanoma solid tumors (199 patients) in Trial CA209003, and review of the 90-day Safety Update. The Applicant was queried on the occurrence of immune-mediated adverse events (AEs) and provided summary AEs from other completed and ongoing studies with nivolumab from the Applicant safety database, which included a total of 1524 patients from studies CA209037, CA209038, CA209066, MDX1106-03, CA209063, CA209017, CA209057, and CA209025 with a data cut-off on July 29, 2014.

The demographics and baseline characteristics of the study population in the nivolumab group vs. the investigator's choice group were: 65% vs. 64% male, median age of 59 vs. 62 years, 98% white, and baseline ECOG performance status 0 (60% vs. 63%) or 1 (40% vs. 36%), 75% vs. 77% with M1c stage disease at study entry; 73% with cutaneous melanoma and 10% with mucosal melanoma. The number of prior systemic regimens received was one for 27% of patients, 2 for 51% of patients, and >2 for 21% of patients. Nineteen percent vs. 13% of patients had brain metastasis and 51% vs. 35% had an elevated an LDH greater than ULN at baseline. The trial excluded patients with active autoimmune disease, ocular melanoma, or a a medical condition that required treatment with corticosteroids or immunosuppression, and /or a history of severe ipilimumab-related adverse reactions. Ipilimumb-related adverse reactions included any CTCAE v4.0 Grade 4 toxicity except resolved nausea, fatigue, infusion reactions or endocrinopathies where symptoms are controlled with hormone replacement therapy, any Grade 3 toxicity unless resolved or controlled within 12 weeks, Grade 2 or greater toxicity of eye pain or reduction in visual acuity that did not improve with topical therapy within 2 weeks or that required systemic treatment, or patients who required infliximab or other immune suppressants.

The median duration of therapy was 5.3 months in the nivolumab group compared to 2.0 months in the investigator's choice group (1.5 months for dacarbazine and 2.9 months with carboplatin and paclitaxel). Patients treated with nivolumab received a median of eight doses and patients treated with dacarbazine received a median of three doses and with carboplatin and paclitaxel a median of five doses. The median cumulative dose of nivolumab, dacarbazine, carboplatin, and paclitaxel was 23.8 mg/kg, 3002.5 mg/m^2, 23.7 mg/kg, and AUC 705.6 respectively. The relative dose intensity of ≥ 90% was achieved in 84.0% of patients treated with nivolumab compared to 71.1% with dacarbazine, 33.3% with carboplatin, and 54.4% with paclitaxel. (Refer to Section 7.2.1)

A higher proportion of patients died in the nivolumab group (25%, 67 patients) compared to the patients in the investigator's choice group (23.5%, 24 patients). The majority of deaths were due to disease progression in the nivolumab group (63 patients,

23.5%) and the investigator's choice group (23 patients, 22.5%) (Refer to Section 7.3.1).

Nonfatal serious adverse events (SAEs) up to 100 days after the last dose of study drug therapy, regardless of causality, were higher in the nivolumab group (50.4%, 135 patients) compared to the investigator's choice group (30.4%, 31patients). In the nivolumab group, most SAEs occurred in ≤ 2% of patients, except for malignant neoplasm progression (20.9%), metastatic malignant melanoma (2.6%), and back pain (2.2%). In the investigator's choice group, the most frequently occurring SAEs (> 2%) were malignant neoplasm progression (12.7%), and dyspnea (2.9%) (Refer to Section 7.3.2).

Grade 3 and 4 AEs which occurred up to 100 days occurred in 113 (42.2%) patients in the nivolumab group compared to 51 (50%) patients in the investigator's choice group. The most frequent (≥2%) Grade 3-4 AEs in the nivolumab group were malignant neoplasm progression (7.8%, 21 patients), anemia (4.9%, 13 patients), abdominal pain (3.4%, nine patients), hyponatremia (2.6%, seven patients), and six patients each with vomiting, general physical health deterioration, increased aspartate aminotransferase, and increased lipase (2.2%) (Refer to Section 7.3.4).

The most common AEs (≥ 20%) in the nivolumab group compared to the investigator's choice group were fatigue (38.8% vs. 43.1%), nausea (23.9% vs. 42.2%) and diarrhea (20.1% vs. 16.7%) (Refer to Section 7.4.1).

The safety profile of nivolumab is acceptable in patients with melanoma who have progressed after treatment with ipilimumab, and a BRAF indicator, if BRAF V600 mutation positive as this is a severe and life-threatening disease. The size of the safety database and duration of nivolumab exposure were sufficient to characterize the safety of nivolumab for treatment of a serious and life-threatening condition with the expectation of updated safety data from the ongoing Phase 3 trial. This reviewer does not recommend a risk evaluation and mitigation strategy (REMS) given the current safety profile of nivolumab and the experience of the medical community in managing immune-mediated adverse reactions based on use of other FDA-approved immune-modulating agents such as ipilimumab. Recommendations for safe and effective use of nivolumab, including monitoring for immune-mediated adverse events, will be made in labeling, including a patient medication guide.

7.1 Methods

The safety of nivolumab in patients with melanoma was primarily evaluated in Trial CA209037 which is based on the cut-off date for the data provided of March 10, 2014 with a clinical database lock date of April 30, 2014. The safety review was supplemented with an evaluation of patients with melanoma and non-melanoma indications treated on Trial CA209003 with a cutoff date of February 4, 2013. Review of

the 90-day safety update provided additional information from the date of database lock for Trial CA209037 until the database lock date of July 29, 2014.

The Applicant mapped and coded verbatim adverse events (AE) terms for Trial CA209037 using MedDRA version 16.1 and for Trial CA209003 using MedDRA version 15.1.

Reviewer Comments:
1. There were discrepancies identified between the datasets and the information provided in the Clinical Study Report. Additional narratives were requested and reviewed. There were no significant issues identified.
2. The Applicant's categorization of data and coding methods were deemed appropriate.
4. The Applicant did not submit an ISS dataset with pooling of both Trials CA209037 and CA209003 due to the different MedDRA and NCI CTCAE versions used in the two trials. The safety was examined in an integrated manner.
5. The Applicant was queried on the occurrence of specific immune-mediated AEs and provided specific AE information from other completed and ongoing studies with nivolumab from the Applicant safety database, which included a total of 1524 patients from studies CA209037, CA209038, CA209066, MDX1106-03, CA209063, CA209017, CA209057, and CA209025 with a data cut-off on July 29, 2014 (Applicant Response to 11/10/2014 FDA Information Request).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review is primarily analyzed from data from Trial CA209037. Trial CA209037 is an open-label, randomize (2:1), Phase 3 study of nivolumab 3 mg/kg Q2W and investigator's choice (dacarbazine or carboplatin and paclitaxel) in unresectable or metastatic melanoma who progressed on or after anti-CTLA-4 therapy, and for those with BRAF V600 mutations, who progressed on or after a BRAF inhibitor in addition to anti-CTLA-4-therapy. The clinical review of safety focused on 370 treated patients, 268 patients in the nivolumab group treated at a dose of 3 mg/kg intravenously Q2W and 102 patients in the investigator's choice group treated with either dacarbazine (N=45) or carboplatin/paclitaxel therapy (N=57). The 370 treated patients are referred to as the All Treated Population in the Clinical Review of Safety. The safety population in the All Treated Population consisted of patients who had been treated with at least one dose of study drug and included 268 patients in the nivolumab group and 102 patients in the investigator's choice group. Safety and exposure included all treated patients in the database and was not restricted based on a 6-month minimum follow-up. The analyses with a 30-day window are the primary analyses of safety for the common AEs. The SAE analyses are conducted using a 100-day window which assesses differences in safety due to potentially late-occurring AEs.

Supportive safety data is provided from Trial CA209003 which is a Phase 1b, open-label, dose-escalation study of different doses of nivolumab in multiple tumors in selected advanced or recurrent malignancies, including melanoma. Trial CA209003 had 306 patients, 107 with melanoma and 199 with non-melanoma indications. The 107 patients with melanoma were treated with nivolumab doses ranging from 0.1 to 10 mg/kg, with 17 patients treated at the dose of 3 mg/kg Q2W. Safety data was reviewed in the 306 patients at the doses at or below the dose proposed for the indication (0.1mg/kg, N=17; 0.3mg/kg, N=18; 1mg/kg, N=86, 3mg/kg, N=54) as supportive data for safety.

Estimates for specific AEs were requested from the Applicant which was provided from the Applicant's safety database which included studies using single-agent nivolumab in 1524 patients.

As requested by the FDA, the Applicant submitted the 4-month safety update as a 90-day safety update.

Reviewer Comments:

1. *The total number of patients treated with single-agent nivolumab 3 mg/kg Q2W was stated as 1800 in the BLA submission. The Applicant clarified that the safety database for single-agent nivolumab identified the following studies: CA209037, CA209038, CA209066, MDX-1106-03, CA209063, CA209017, CA209057, and CA209025 (Applicant Response to 11/3/2014 FDA Information Request). At a data cutoff date of July 29, 2014, a total of 1524 patients had received single-agent nivolumab. The Applicant stated that Study CA209067 was excluded because the study is still ongoing and blinded (1826 minus 302 from CA209067).*
2. *The size of the safety database and duration of nivolumab exposure were sufficient to characterize the safety of nivolumab for treatment of a serious and life-threatening condition with the expectation of updated safety data from the ongoing Phase 3 trial.*

7.1.2 Categorization of Adverse Events

The Applicant graded the severity of AEs observed on Trial CA209037 using NCI CTCAE version 4.0, and for Trial CA209003 using NCI CTCAE version 3.0. The Applicant mapped and coded verbatim AE terms for Trial CA209037 using the MedDRA version 16.1 and for Trial CA209003 using MedDRA version 15.1.

Reviewer Comments:

1. *The clinical review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the CA209037 raw AE dataset and 20% of the CA209003 raw AE dataset. Of the 4,991 AE line listings in the CA209037 AE.xpt dataset, the review used manual*

matching of all verbatim and MedDRA PTs to assess the acceptability of the Applicant's mapping from the verbatim term to MedDRA PT. The MedDRA PTs listed in both datasets adequately represented the investigator recorded term (i.e., verbatim term) and did not raise any significant issues.

2. *The clinical review of safety included an audit of AE case report forms randomly in 10% of cases to assess the completeness and verify the accuracy of the raw AE datasets. The review did not raise any significant issues.*

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling of data across the two trials, CA209037 and CA209003, was not performed by the Applicant.

Reviewer Comment:
FDA agreed with the applicant that pooling of the data was not required for this application based on the difference in the two trials with respect to the patient population.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The total number of patients treated with single-agent nivolumab 3 mg/kg Q2W across multiple studies and indications is approximately 1524. The primary analyses of the safety profile of nivolumab 3mg/kg Q2W in patients with advanced melanoma is derived from 268 patients treated in Trial CA209037 supported by 306 patients treated in Trial CA209003, which included 107 patients with melanoma.

In the All Treated Population, 268 patients received treatment with nivolumab and 102 patients received treatment with investigator's choice. The median duration of therapy was 5.3 months in the nivolumab group compared to 2.0 months in the investigator's choice group (1.5 months for dacarbazine and 2.9 months with carboplatin and paclitaxel). Patients treated with nivolumab received a median of eight doses and patients treated with dacarbazine received a median of three doses and with carboplatin and paclitaxel a median of five doses. The median cumulative dose of nivolumab, dacarbazine, carboplatin, and paclitaxel was 23.8 mg/kg, 3002.5 mg/m2 , 23.7 mg/kg, and AUC 705.6 respectively. The relative dose intensity of ≥ 90% was achieved in 84.0% of patients treated with nivolumab compared to 71.1% with dacarbazine, 33.3% with carboplatin, and 54.4% with paclitaxel. Table 22 shows the summary of exposure to the study drugs.

Table 22: Summary of Exposure (All Treated Population)

	Nivolumab N=268	Dacarbazine N=45	Carboplatin N=57	Paclitaxel N=57
Number of Doses Received				
Mean (SD)	9.4 (6.7)	3.7 (2.2)	4.6 (2.2)	4.6 (2.2)
Median (Min, Max)	8 (1, 31)	3 (1, 11)	5 (1, 11)	5 (1, 11)
Cumulative Dose				
Mean (SD)	28.1 (20.1)	3655.7 (2279.6)	23.7 (12.6)	752.2 (359.0)
Median (Min, Max)	23.8 (3, 93.1)	3002.5 (993.2, 11045.6)	23.7 (4.9, 54.0)	705.6 (171.4, 1611.2)
Relative Dose Intensity				
90% to < 110%	225 (84.0)	32 (71.1)	19 (33.3)	31 (54.4)
70% to < 90%	38 (14.2)	10 (22.2)	26 (45.6)	21 (36.8)
50% to < 70%	5 (1.9)	2 (4.4)	9 (15.8)	5 (8.8)
< 50%	0	0	3 (5.3)	0

Source: ADEXS.xpt
Dose units for nivolumab are in mg/kg, for dacarbazine and paclitaxel in mg/m2, and for carboplatin AUC.

Demographics and baseline characteristics within each treatment group in the All Treated population were well matched. The study population characteristics in the nivolumab group vs. the chemotherapy group were: 65% vs. 64% male, median age of 59 vs. 62 years, 98% white, baseline ECOG performance status 0 (60% vs. 63%) or 1 (40% vs. 36%), 75% vs. 77% with M1c stage disease; 73% with cutaneous melanoma and 10% with mucosal melanoma; The number of prior systemic regimens received was 1 for 27% of patients, 2 for 51% of patients, and >2 for 21% of patients, 22% of patients in both groups were BRAF V600 mutation positive and 49% vs. 50% of patients were PD L1 positive. Sixty-four percent of patients had no prior clinical benefit (CR/PR or SD) on ipilimumab. 19% vs.13% had brain metastasis and 51% vs. 35% had an elevated LDH. The trial excluded patients with active autoimmune disease, ocular melanoma, or a medical condition that required treatment with corticosteroids or immunosuppression, and /or a history of severe ipilimumab-related adverse reactions. Ipilimumb-related adverse reactions included any CTCAE v4.0 Grade 4 toxicity except resolved nausea, fatigue, infusion reactions or endocrinopathies where symptoms are controlled with hormone replacement therapy, any Grade 3 toxicity unless resolved or controlled within 12 weeks, Grade 2 or greater toxicity of eye pain or reduction in visual acuity that did not improve with topical therapy within 2 weeks or that required systemic treatment, or patients who required infliximab or other immune suppressants.

At the time of the 90-day Safety Update database lock, 37.7% of patients were continuing with study treatment in the nivolumab group compared to 8.8% in the investigator's choice group. The median cumulative dose of nivolumab increased from 23.8 mg/kg to 30.0 mg/kg, and the median number of doses received increased from 8.0 to 10.0.

In Trial CA209003, patients with melanoma were exposed to nivolumab up to 2.3 years at the database lock date.

Reviewer Comments:
1. The size of the safety database and duration of nivolumab exposure were sufficient to characterize the safety of nivolumab for treatment of a serious and life-threatening condition with the expectation of updated safety data from the ongoing Phase 3 trial, CA209037.

7.2.2 Explorations for Dose Response

Refer to Section 7.5.1 for explorations of exposure-response relationships for AEs.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the summary of the Pharmacology/Toxicology Review in Section 4.3.

7.2.4 Routine Clinical Testing

The routine clinical testing of patients enrolled in the clinical trials, including efforts to elicit adverse event data by monitoring laboratory tests, vital signs, and oxygen saturation appear to have been adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to the summary of the Clinical Pharmacology Review in Section 4.4.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The adverse events known to be associated with anti-PD-1 / anti-PD-L1 drugs, including pembrolizumab which was approved by the FDA on September 4, 2014 are primarily immune-mediated reactions and include pneumonitis, colitis, hepatitis, hypophysitis, renal failure, nephritis, hyperthyroidism, and hypothyroidism. The Applicant identified select AE categories in the application to characterize AEs of special clinical interest. These included endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash which were grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively. Infusion reactions were also included. The Applicant also identified select AEs of special interest based on AEs which may require immunosuppression as part of their management. Refer to Section 7.3.2 for details.

7.3 Major Safety Results

7.3.1 Deaths

Deaths listed include deaths during treatment and occurring up to 100 days of last dose of study drug as of the database lock date (April 30, 2014).

A higher proportion of patients died in the nivolumab group (25%, 67 patients) compared to the patients in the investigator's choice group (23.5%, 24 patients). The majority of deaths were due to disease progression in the nivolumab group (63 patients, 23.5%) and the investigator's choice group (23 patients, 22.5%). Table 23 summarizes the primary causes of death for patients in the all treated safety population in Trial CA209037.

Table 23: Summary of Deaths (All Treated Population)

Primary Cause of Death	Nivolumab N=268 (%)	Investigator's Choice N=102 (%)
Patients who Died	67 (25)	24 (23.5)
Disease Progression	63 (23.5)	23 (22.5)
Other	3 (1.1)	1 (1.0)
Unknown	1 (0.4)	0
30 Days of Last Dose		
Disease Progression	26 (9.7)	2 (2.0)
Other	2 (0.7)	0
100 Days of Last Dose		
Disease Progression	57 (21.3)	14 (13.7)
Other	3(1.1)	1 (1.0)
Unknown	1(0.4)	0

Source: ADAE.xpt, ADSL.xpt

In Trial CA209037, five patients died for reasons other than disease progression. The investigator classified the primary reason for death as 'other' (i.e., not study drug toxicity, disease progression, or unknown) for three (1.1%) patients in the nivolumab group and one (1%) patient in the investigator's choice group. The primary reason for death was 'unknown' for one (0.4%) patient in the nivolumab group. Table 24 summarizes the narratives for the patients with reasons for death other than disease progression.

Table 24: Narratives for Deaths Other than Disease Progression (All Treated Population)

Patient ID	Summary of Case	Reviewer Comment

CA209037-28-37407	71 year-old female with a history of adrenal insufficiency requiring oral prednisone at a dose of 5 mg/day which had been started 21 days prior to the first dose of nivolumab and the prednisone was continued during the trial. The patient had a first episode of Grade 2 hypoxia on Day 15 after the first dose of nivolumab. Study drug was delayed, the hypoxia resolved, and nivolumab was resumed on Day 20. On Day 67, five days after the fifth dose of nivolumab, patient had disease progression with new lesions in the lung, liver, and soft tissue. The patient continued to receive nivolumab beyond progression. On Day 86, ten days after the sixth dose of nivolumab, the patient was hospitalized for Grade 2 pyrexia. Chest x-ray showed increased bilateral diffuse reticulonodular opacities. Nivolumab was discontinued on Day 88 and the patient was discharged on Day 90. On Day 97, the patient was hospitalized for a right femur fracture. She was hypoxic at rest and stated to have hypoxia for two months. Chest x−ray showed abnormal diffuse reticular nodular interstitial pattern through all lung segments. CT and pulmonary angiography showed extensive metastatic disease in the pulmonary parenchyma, borderline-enlarged mediastinal and hilar lymph nodes, probable liver metastases, but no pulmonary embolism. There was lower lobe airspace disease suspicious for pneumonia, geographic ground-glass density which was a possible manifestation of atypical infection, non-cardiogenic edema, or hemorrhage, but reported no conclusive evidence of pneumonitis. A bronchoscopy was not performed. High-dose steroids were administered as treatment for possible pneumonitis. On Day 108, a repeat chest x-ray showed tiny nodular infiltrates throughout the lungs. On Day 111, the patient was re-hospitalized for hypoxia, which was reported as a serious adverse event considered by the investigator to be related to study therapy. She did not want aggressive measures. On Day 112, the patient died due to hypoxia of multifactorial cause. Her death was considered by the investigator to be at least possibly related to study drug. The cause of death was reported as metastatic melanoma with metastases to the lung and right femur. The investigator classified the death as ‘other’. In the 90-day Safety Update, the cause of death was updated by the investigator to ‘disease progression’.	Although the patient had progressive disease in the lungs, the hypoxia started on Day 15, resolved after nivolumab dose was withheld, and was present for two months prior to Day 97 during continued treatment. It could be possibly related to nivolumab. Note that nivolumab was continued in this patient after protocol-specified tumor assessments showed progressive disease.

CA209037-24-37631	66 year-old male who was hospitalized on Day 36, eight days after the third dose of nivolumab, for Grade 3 back pain, resulting from a Grade 2 spinal compression fracture at T10, L2, and L3, which improved to Grade 1 on Day 42. On Day 43, one day after the fourth dose of nivolumab, disease progression was observed in the lung and lymph nodes and the patient was hospitalized on Day 44 for failure to thrive. Nivolumab was discontinued on day 44. Chest x-ray showed a small right pleural effusion with right lower lobe air space opacification and a Grade 2 adverse event of hypoxia was reported. On Day 50 an MRI scan showed diffuse metastatic disease throughout the thoracic spine. On day 54 the subject died of cardiopulmonary arrest. The investigator classified the death as 'other'.	The death is unlikely related to nivolumab.
CA209037-30-37309	54 year-old female weighing 229 pounds (104 kg) at baseline, with a history of adrenal insufficiency and pituitary prolactinoma (both not related to prior ipilimumab therapy) on hydrocortisone and prednisone. On Day 62, Day 110, and Day 148, protocol specified tumor assessments showed a marked decrease in target lesion size. The last dose of nivolumab was on Day 180, during which her vital signs were stable, ECOG performance status was 0, and weight had increased to 116 kg. On Day 196, 16 days after the fourteenth dose of nivolumab, the patient was found dead in bed in her home. The investigator attributed the death due to pulmonary embolism, later updated to pneumonia. The autopsy report revealed the death due to pneumonia in the setting of metastatic melanoma, with Class III obesity as a contributing condition. Post-mortem bacterial cultures revealed Staphylococcus species coagulase negative, occasional presumptive Clostridium limosum, and viral cultures were unrevealing for Herpes simplex virus, Influenza virus type A or B, Respiratory Syncytial virus, Adenovirus, Parainfluenza virus types 1, 2, 3, and Cytomegalovirus. The investigator classified the death as 'other'. In the 90-day Safety Update, the cause of death was updated by the investigator to pneumonia.	The death due to pneumonia could be possibly related to nivolumab.

CA209037-28-37383	65 year-old male with a history of hypertension, thromboembolic disease, pulmonary embolism, adrenal insufficiency related to prior ipilimumab on hydrocortisone, hypothyroidism related to prior ipilimumab, depression and radiosurgery to brain lesions was hospitalized for Grade 2 dizziness on Day 15, 14 days after the first dose of nivolumab, and found to have orthostatic hypotension. An MRI scan of the brain showed stable appearance of brain metastases, no new intracranial lesions, no acute infarct, and no other acute intracranial abnormality. Chest x-ray showed a new 5-mm nodule in the right upper lobe (possible metastasis) and a right pleural effusion. The event was treated with acetaminophen, azithromycin, morphine, oxycodone, ondansetron, ceftriaxone, clonazepam, and levothyroxine. No action was taken with regard to study therapy. The event of dizziness resolved, and subsequently the patient was discharged from the hospital on Day 16. On Day 26, 25 days after the first dose of nivolumab, the patient was hospitalized for Grade 2 confusion and hallucinations. An electrocardiogram showed normal sinus rhythm and prolonged QT. A CT scan of the head without contrast showed no evidence of a cerebral or cerebellar mass. The patient mentioned that he had previously experienced a change in mental status after taking clonazepam together with quetiapine. The confusion resolved on discontinuing clonazepam and he was discharged on Day 27. No action was taken with regard to study therapy. On Day 34, 33 days after the first dose of nivolumab, the patient died due to an unknown cause. The investigator classified the death as 'unknown'. After the hospital discharge, the investigator did not report any visits or treatments prior to the reported death on Day 34. The patient's friend called to report that the patient was found dead at home. The certificate of death recorded gastric carcinoma (Applicant Response to 10/31/2014 and 11/29/2014 FDA Information Request). In the 90-day Safety Update, the cause of death was updated to 'disease progression' by the investigator.	Disease progression
CA209037-110-37543	81-year-old male in the investigator's choice group receiving two doses of dacarbazine and tumor assessment on Day 55 revealed progression, including CNS lesions. On Day 91, the patient experienced multi-organ failure considered by the investigator to be related to melanoma, including renal and liver failure. The primary reason for death was classified as 'other' by the investigator.	Disease progression.

Source: Narratives; Applicant Response to 9/17/2014 FDA Information Request, 10/31/2014 FDA Information Request

Grade 5 AEs occurred in 44 (16.4%) patients in the nivolumab group and 13 (12.7%) patients in the investigator's choice group. In the nivolumab group, 38/44 patients had Grade 5 AEs attributed to malignant neoplasm progression or metastatic malignant melanoma, and 12/13 patients in the investigator's choice group were attributed to

malignant neoplasm progression. There were six Grade 5 AEs in the nivolumab group that were not attributed to disease progression: pneumonia (n=1), cardio-respiratory arrest (n=1), cardiac failure (n=1), sudden death (n=1), death (n=1), and hypoxia (n=1). Details for four patients are provided in Table 6. Of the remaining two patients, one AE was post-obstructive pneumonia secondary to metastatic disease, and cardiac failure attributed to disease progression in the lungs.

Table 25 summarizes the Grade 5 AEs that occurred in the nivolumab group. The investigators reported that all were unrelated to nivolumab.

Table 25: Grade 5 Adverse Events Other than Disease Progression (All Treated Population)

Patient ID	Age/Sex	Adverse Events	Last Dose (Day)	Onset (Day)	Death (Day)	Investigator Reported Primary Cause of Death
CA209037-14-37211	63/M	Pneumonia	31	36	36	Disease
CA209037-24-37631*	66/M	Cardio-respiratory arrest	44	54	54	Cardio-pulmonary arrest
CA209037-28-37383*	65/M	Death	1	34	34	Disease
CA209037-28-37407*	71/F	Hypoxia	88	111	111	Hypoxia
CA209037-30-37309*	54/M	Sudden death	180	196	196	Sudden death due to probable pulmonary embolism
CA209037-9-37286	54/M	Cardiac failure	25	71	71	Disease

Source: ADAE.xpt, Narratives, Case Report Forms, Applicant Response to 9/17/2014 FDA Information Request.
*Details of Grade 5 AEs provided in Table 6

Additional details were requested from the Applicant for the following patients:

CA209037-14-37211: The patient was hospitalized for Grade 3 productive cough with hemoptysis on Day 13, 12 days after the first dose of nivolumab, considered by the investigator to be not related to study drug. He also had weakness and fever with a high white blood cell count. A chest X-ray showed findings suspicious for post-obstructive pneumonia secondary to metastatic disease, including worsening partial opacification of the left chest due to moderate pleural effusion and partial lung collapse. No action was taken with regard to study therapy. Antibiotics were administered and on Day 15, the event resolved. On Day 31, 14 days after the second nivolumab dose, the patient was re-hospitalized for Grade 3 post-obstructive pneumonia and dehydration which were considered by the investigator to be not related to study therapy. A chest x-ray showed an increase in the large left pleural effusion with only partial aeration of the

left upper lobe. The patient was diagnosed with clinical disease progression. The dose of nivolumab was withheld. Antibiotics were administered. On Day 33 the patient was discharged to hospice care where the patient died due to Grade 5 obstructive pneumonia on Day 36, which was considered by the investigator to be not related to study therapy. The investigator attributed the death to disease progression with post-obstructive pneumonia.

CA209037-9-37286: The patient was hospitalized for Grade 2 dyspnea on Day 16, 15 days after the first dose of nivolumab. Study therapy was delayed. The patient was treated with IV hydrocortisone 200 mg for 5 days and oral prednisone at 40 mg/day. Dyspnea improved. Tumor assessment showed an increase in the size of the left lung lesion, new pleural effusion and new ascites. Dyspnea was considered due to disease progression. On Day 31, six days after the second dose of nivolumab, the patient was re-hospitalized for Grade 2 dyspnea which resolved after 3 days. On Day 50, the patient was hospitalized for Grade 4 heart failure attributed to disease progression in the lungs. On Day 71, the patient died due to Grade 5 heart failure.

CA209037-50-37189: 63-year old male with stage IV cutaneous melanoma, M1c status, BRAF mutation-positive, with metastases to the lymph node, liver, lung, spleen, and bone at the time of enrollment into the study with pretreatment tachycardia (Grade 1), decreased breath sounds in the left lung, and decreased oxygen saturation (92%) on exertion at baseline. During study therapy, the patient continued to have worsening non-related adverse events including Grade 2 fatigue, Grade 2 dyspnea, Grade 2 ascites, and Grade 2 decreased appetite. After two doses of treatment the patient was referred for home nursing care to receive supplemental oxygen for treatment of shortness of breath. Following decline in performance status, on Day 26, 11 days after the second dose of nivolumab, the patient was hospitalized for Grade 4 cardiac arrest which was considered by the investigator to be related to disease progression and not related to study therapy. He was resuscitated and placed on mechanical ventilation in the intensive care unit, and subsequently died later that same day due to malignant neoplasm progression considered by the investigator to be not related to study therapy. The Applicant clarified that the investigator reported a rapid progression of liver metastasis (Applicant Response to 12/3/2014 FDA Information Request).

To determine if any of the early deaths attributed to melanoma disease progression by the investigators were also associated with drug-related SAEs, the Applicant reviewed all deaths that occurred within the first nine weeks (63 days) of treatment (prior to first on-study tumor assessment). There were 34 deaths within the first 9 weeks, of which 29 were in the nivolumab group and five were in the investigator's choice group. Of the 29 deaths within the first nine weeks of treatment in the nivolumab group, 27 were due to melanoma disease progression and two were not due to disease progression. Of the 27 deaths due to disease progression, three subjects had SAEs other than malignant neoplasm progression with an outcome of death: CA209037-14-37211 experienced unrelated obstructive pneumonia; CA209037-16-37419 experienced unrelated hypotension and unrelated atrial fibrillation; and CA209037-50-37189 experienced unrelated cardiac arrest. Of the two deaths that were not due to disease progression: CA209037-24-37631 was due to unrelated cardiopulmonary arrest; CA209037-28-37383 was recorded as due to an unknown cause. The Applicant provided additional information in a response to FDA Information Request dated October 31, 2014, which described a radiology report with a new right upper lobe nodule and possible metastasis, and a new right pleural effusion.

The Applicant's explanation for the higher deaths in the nivolumab group is the longer duration of treatment in the nivolumab group compared to the investigator's choice group.

In the 90-day Safety Update, study drug toxicity was not reported as the primary reason for death by the investigators in either treatment group. The primary reason for death in the nivolumab group was reported as 'other' in two patients. Patient CA209037-33-37582 was a 43 year old male who died of Pneumocyctis jiroveci pneumonia 80 days after the last dose of nivolumab. CA209037-59-37582 was a 61 year old male who died due to disease progression and demyelination 205 days after the last dose of nivolumab.

In Trial CA209003, as of database lock, 75 deaths (24.5%) were reported during treatment or up to 100 days of the last dose of nivolumab. The majority of the deaths were due to malignant disease (22.9%, 70 patients). In the 107 patients in the melanoma group, 19 (17.8%) patients died within 100 days of the last dose, none of which were considered to be drug related by the Applicant. All 19 were due to malignant disease.

Five (1.7%) patients died in Trial CA209003 due to pneumonitis. Three patients in Trial CA209003 developed pneumonitis within 100 days of last dose of nivolumab (two with NSCLC [CA209003-1-699 (Grade 4) and CA209003-5-710 (Grade 4)], and one with CRC [CA209003-1-3582 (Grade 2)]). The three patients died after developing subsequent AEs of sepsis or respiratory failure. In the first two patients, there was a delay of approximately 1 to 2 weeks between the onset of symptoms and treatment with high doses of corticosteroids. In the third patient, corticosteroids were provided with an

initial improvement of symptoms; however, the taper was rapid. The Applicant reported two additional patient deaths due to pneumonitis (two with NSCLC [CA209003-1-603 and CA209003-8-695]) after greater than 100 days after the last dose of nivolumab. Two patients received treatment with 1 mg/kg of nivolumab, two patients received 3 mg/kg, and one patient received 10 mg/kg of nivolumab. All the deaths were considered related to the study drug by the investigator.

The first four events of pneumonitis, three of which were Grade 3 or 4, occurred prior to the implementation of the pulmonary AE guideline. The Applicant subsequently instituted a management algorithm for pulmonary toxicity which addressed the need for early intervention with corticosteroids in symptomatic patients along with the need for an extended taper. The Applicant states that across all other completed and ongoing studies with single-agent nivolumab, the vast majority of which were started after the pulmonary toxicity management algorithm was implemented, a case of fatal pneumonitis was reported in Study CA209039 in relapsed or refractory hematologic malignancies. The guideline for the management of pulmonary toxicity was provided to all investigators in version 7 (August 27, 2011) of the Investigator's Brochure, which was in place at the time of initiation of Trial CA209037.

Reviewer's Comments:

1. *The reviewer did not agree with the Applicant on the Grade 5 AE onset date recorded in the dataset based on the case narratives as noted:*
    - *For patient CA209037-28-37407, the start date of hypoxia was recorded as Day 111 in the dataset. However, the first instance of hypoxia was reported by the patient on Day 15. Although the patient had progressive disease in the lungs, when she was hospitalized on Day 88, she had hypoxia on rest and reported hypoxia for two months, during which she continued treatment with nivolumab. The hypoxia could be possibly related to nivolumab. Note that nivolumab was continued in this patient after protocol-specified tumor assessments showed progressive disease.*
    - *For patient 209037-9-37286, the start date of cardiac failure was recorded as Day 71 in the dataset. However, on Day 16, 15 days after the first dose of nivolumab, the patient was hospitalized for Grade 2 dyspnea, which was considered due to disease progression in the lungs. The patient was continued on treatment and on Day 31, six days after the second dose of nivolumab, the patient was re-hospitalized for Grade 2 dyspnea which resolved and the patient was discharged on Day 33. On Day 50, 25 days after the second dose of nivolumab, the patient was hospitalized for Grade 4 heart failure which the investigator attributed to disease progression. On Day 71, the patient died due to Grade 5 heart failure. Thus the event of heart failure was ongoing since day 50.*
    - *For patient CA209037-14-37211, the start of pneumonia was recorded as Day 36 in the dataset. However, on Day 13, 12 days after the first dose of nivolumab, the patient was hospitalized for a Grade 3 productive cough*

with hemoptysis, weakness, and fever which resolved on Day 15. On Day 31, 14 days after the second dose of nivolumab, the patient was hospitalized again for Grade 3 post-obstructive pneumonia and dehydration. The patient was subsequently discharged to hospice care and his death on Day 36 was attributed to disease progression with post-obstructive pneumonia. Thus the event of post-obstructive pneumonia was ongoing since Day 31.

2. *The death of patient CA209037-50-37189 describes a Grade 4 cardiac arrest and also death on the same day attributed to disease progression. The Applicant was queried to explain why the cardiac arrest is not attributed to nivolumab. The investigator confirmed that the patient had rapid progression of his liver metastases and expired due to disease and therefore attributed the cardiac arrest to disease progression rather than study drug toxicity (Applicant Response to 9/17/2014 FDA Information Request).*
3. *Four out of the five patients who died due to pneumonitis had NSCLC and three patients died of sepsis. Four patients had bronchoscopy which initially ruled out infectious etiology. Evaluation of pneumonitis in patients with NSCLC and pulmonary metastases can be challenging. Pneumonitis can have highly variable appearances on radiographic images. Despite the initiation of a pneumonitis management algorithm for early recognition and management of pneumonitis, an additional patient died in another study. The reviewer recommends a boxed warning in the label for pneumonitis.*
4. *Four out of the six patients with Grade 5 deaths required multiple post-verification CRF updates by the Applicant.*
5. *Additional narratives were requested for nine patients treated with nivolumab reported to have died due to disease progression as an audit. Audit review of the cases were consistent with the Applicant's assessment of disease progression.*

7.3.2 Nonfatal Serious Adverse Events

Nonfatal SAEs of any grade up to 100 days after the last dose of study therapy, regardless of causality, were higher in the nivolumab group (50.4%, 135 patients) compared to the investigator's choice group (30.4%, 31patients). In the nivolumab group, most SAEs occurred in ≤ 2% of patients, except for malignant neoplasm progression (20.9%), metastatic malignant melanoma (2.6%), and back pain (2.2%). In the investigator's choice group, most frequently reported SAEs (> 2%) reported were malignant neoplasm progression (12.7%), and dyspnea (2.9%). SAEs that result in death are discussed in Section 7.3.1. Table 26 summarizes the nonfatal and fatal SAEs that occurred in ≥ 1% patients in the nivolumab group.

Table 26: Serious Adverse Events in ≥1% (All Treated Population)

System Organ Class Preferred Term	Nivolumab N=268			Investigator's Choice N=102		
	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)	Any Grade n (%)	Grade 3-4 n (%)	Grade 5 n (%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)						
Malignant Neoplasm Progression	56 (20.9)	19 (7.1)	36 (13.4)	13 (12.7)	1 (1.0)	12 (11.8)
Metastatic Malignant Melanoma	7 (2.6)	5 (1.9)	2 (0.7)	0	0	0
Musculoskeletal And Connective Tissue Disorders						
Back Pain	6 (2.2)	5 (1.9)	0	2 (2.0)	1 (1.0)	0
Gastrointestinal Disorders						
Abdominal Pain	5 (1.9)	5 (1.9)	0	1 (1.0)	1 (1.0)	0
Diarrhea	3 (1.1)	3 (1.1)	0	1 (1.0)	1 (1.0)	0
General Disorders And Administration Site Conditions						
General Physical Health Deterioration	5 (1.9)	5 (1.9)	0	0	0	0
Cardiac Disorders						
Atrial Fibrillation	4 (1.5)	3 (1.1)	0	0	0	0
Cardiac Arrest*	3 (1.1)	3 (1.1)	0	0	0	0
Infections And Infestations						
Sepsis	4 (1.5)	4 (1.5)	0	0	0	0
Pneumonia	3 (1.1)	2 (0.7)	1 (0.4)	0	0	0
Urinary Tract Infection	3 (1.1)	3 (1.1)	0	0	0	0
Respiratory, Thoracic And Mediastinal Disorders						
Dyspnea	4 (1.5)	1 (0.4)	0	3 (2.9)	2 (2.0)	0
Metabolism And Nutrition Disorders						
Dehydration	3 (1.1)	3 (1.1)	0	0	0	0
Vascular Disorders						
Hypotension	3 (1.1)	3 (1.1)	0	1 (1.0)	1 (1.0)	0

Source: ADAE.xpt
*Cardiac arrest includes cardio-respiratory arrest

Select Adverse Events

A list of the Select AEs were provided in the core safety SAP and included the following categories: Endocrine AEs, gastrointestinal AEs, hepatic AEs, pulmonary AEs, renal AEs, skin AEs, and hypersensitivity/infusion reactions. Select AEs included immune-related AEs, AEs that may differ from or be more severe than AEs caused by non-immunotherapies and AEs whose early recognition and management may mitigate severe toxicity. In addition to the frequency and worst severity of select AEs, time-to onset, time-to resolution and time-to resolution where immune modulating medication was initiated were analyzed for each specific category.

In the initial trials conducted by the Applicant, safety management guidelines were based on prior experience with ipilimumab, and included the management of toxicities that were expected to be encountered, including gastrointestinal, endocrine, and hepatic AEs. During the course of Trial CA209003, management guidelines for pulmonary and renal AEs were added once the occurrence of these events, in some cases requiring immunosuppressive medications for management, was reported. The Applicant states that the AE profile reported for Trial CA209037 reflects the expected profile when current management recommendations are implemented.

Adverse events belonging to a Select AE category may require treatment with corticosteroids or, if refractory to corticosteroids, other immunosuppressive medications. In order to ensure consistent guidance, safety management guidelines for AEs potentially requiring such management were included in the Investigator Brochure version 12. The guidelines include corticosteroid dose and duration recommendations. Recommendations for corticosteroid dose are specific to the type and severity of the AE being treated.

Among patients treated in Trial CA209037, the most frequently occurring (≥ 10%) Select AE categories in the nivolumab group were skin (35.8%), gastrointestinal (21.3%), endocrine (11.9%), and hepatic (11.2%), followed by renal (6.7%), pulmonary (3.4%), and hypersensitivity/infusion reactions (3.0%). With the exception of hypersensitivity/infusion reactions, higher frequencies of events occurred in the nivolumab group compared with the investigator's choice group in select AE categories as shown in Table 27.

Table 27: Summary of Select Adverse Event Categories (All Treated Population)

Select AE Category	Nivolumab N=268 n (%)	Investigator's choice N=102 n (%)
Total Events	**158 (59.0)**	**41 (40.2)**
Skin Adverse Event	96 (35.8)	17 (16.7)
Gastrointestinal Adverse Event	57 (21.3)	18 (17.6)
Endocrine Adverse Event	32 (11.9)	2 (2.0)
Hepatic Adverse Event	30 (11.2)	8 (7.8)
Renal Adverse Event	18 (6.7)	4 (3.9)
Pulmonary Adverse Event	9 (3.4)	0
Hypersensitivity/Infusion Reaction	8 (3.0)	8 (7.8)

Source: ADAE.xpt

Skin Select AEs

The Applicant included the following terms: blister, dermatitis, dermatitis exfoliative, drug eruption, eczema, erythema, erythema multiform, exfoliative rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, pruritus, pruritus allergic, pruritus generalized, psoriasis, rash, rash erythematous, rash generalized, rash

macular, rash maculo-papular, rash papular, rash pruritic, skin exfoliation, skin hypopigmentation, skin irritation, Steve-Johnson Syndrome, toxic epidermal necrolysis, urticaria, and vitiligo, in the skin Select AE category, terms that would encompass AEs considered most likely to be reported in a patient with rash. The reviewer also included the following terms: dermatitis acneiform, dermatitis allergic, rash follicular, rash pustular, rash vesicular, and skin pigmentation; and extended the time up to 100 days after the last dose of the study drug, leading to the inclusion of four additional patients in the nivolumab group and one additional patient in the investigator's choice group.

The AEs belonging to the skin Select AE category occurred in 96 (35.8%) patients in the nivolumab group and 17 (16.7%) patients in the investigator's choice group. The most frequently occurring AEs (≥ 2% of patients), regardless of causality, were rash, pruritus, vitiligo, and dermatitis in the nivolumab group and rash, pruritus, and photosensitivity reaction in the investigator's choice group. AEs belonging to the skin Select AE category considered drug-related by the investigator were reported in 78 of 96 patients in the nivolumab group and 12 of 15 patients in the investigator's choice group. Table 28 summarizes the skin Select AEs in the All Treated Population.

Table 28: Summary of Skin Adverse Events (All Treated Population)

Adverse Events	**Nivolumab N=268 n (%)**	**Investigator's choice N=102 n (%)**
Total Skin Events	96 (35.8)	17 (16.7)
Rash*	57 (21.3)	7 (6.9)
Pruritus	51 (19.0)	4 (3.9)
Vitiligo	14 (5.2)	0
Dermatitis[#]	6 (2.2)	1 (1.0)
Photosensitivity Reaction	4 (1.5)	2 (2.0)
Dermatitis Acneiform	3 (1.1)	1 (1.0)
Eczema	3 (1.1)	0
Dermatitis Exfoliative	2 (0.7)	0
Erythema	2 (0.7)	1 (1.0)
Skin Exfoliation	2 (0.7)	0
Skin Hypopigmentation	2 (0.7)	1 (1.0)
Urticaria	2 (0.7)	0
Dermatitis Allergic	1 (0.4)	0
Erythema Multiforme	1 (0.4)	0
Psoriasis	1 (0.4)	0
Skin Hyperpigmentation	1 (0.4)	0
Skin Irritation	1 (0.4)	0
Palmar-Plantar Erythrodysesthesia Syndrome	0	1 (1.0)

Source: ADAE.xpt
*Includes a composite of rash maculo-papular, rash erythematous, rash pruritic, rash follicular, rash macular, rash popular, rash pustular, rash vesicular
[#] includes a composite of dermatitis exfoliative and dermatitis acneiform

The AEs were mostly Grade 1-2 in severity in both the nivolumab and investigator's choice groups. One (0.4%) patient in the nivolumab group and none in the investigator's group had a Grade 3/4 AE. The patient (CA209037-43-37151) developed a Grade 3 rash which was reported as a non-serious adverse event considered by the investigator to be related to study therapy. Nivolumab dose was delayed due to the rash. The patient was treated with corticosteroids, the rash resolved, and the patient resumed nivolumab. There were no Grade 4 or Grade 5 AEs, SAEs, or AEs leading to discontinuation in the skin Select AE category.

Reviewer Comment:

1. *Rash is an expected immune-mediated AE and one patient with a Grade 3 rash improved with treatment with corticosteroids.*
2. *The Applicant has established a skin AE management algorithm which has been applied across the nivolumab program and remains appropriate for managing skin AEs. Refer to the Appendix for the skin AE management algorithm.*

Gastrointestinal Select Adverse Event Category

The Applicant identified gastrointestinal Select AEs included the following terms: colitis, colitis ulcerative, diarrhea, enteritis, enterocolitis, frequent bowel movements, and GI perforation, terms selected to encompass those most likely to be reported in a patient with diarrhea or colitis. The reviewer extended the time up to 100 days, leading to the inclusion of two additional patients in the nivolumab group and one additional patient in the investigator's choice group. Adverse event terms belonging to the GI Select AE category occurred in 57 (21.3%) patients in the nivolumab group and 18 (17.6%) patients in the investigator's choice group. Three (1.1%) cases of colitis occurred in the nivolumab group compared to one (1.0%) case in the investigator's choice group. The most frequently occurring AE (≥ 10%), regardless of causality, was diarrhea in both the nivolumab and investigator's choice groups. Drug-related AEs were reported in 32 of 57 patients in the nivolumab group and 15 of 18 patients in the investigator's choice group. Table 29 summarizes the gastrointestinal Select AEs in the All Treated Population.

Table 29: Summary of Gastrointestinal Adverse Events (All Treated Population)

Adverse Event	Nivolumab N=268 n (%)	investigator's choice N=102 n (%)
Total Gastrointestinal AE	57 (21.3)	18 (17.6)
Diarrhea	56 (20.9)	17 (16.7)
Colitis	3 (1.1)	1 (1.0)
Frequent Bowel Movements	1 (0.4)	0

Source: ADAE.xpt

Most patients experienced Grade 1-2 AEs. Five (1.9%) patients experienced Grade 3 colitis or diarrhea in the nivolumab group and two (1.9%) patients in the investigator's choice group. Of the five patients, two (CA209037-15-37264 and CA209067-27-37152) experienced colitis and three patients (CA209037-13-37161, CA209037-39-37563, and CA209037-62-37365) experienced diarrhea. Three of the AEs, two colitis and one diarrhea, were considered study drug related by the investigator. No Grade 4 or Grade 5 AEs were reported in either group. Nivolumab dose was delayed in two patients, one each for colitis, and withdrawn for autoimmune colitis in one patient. There were no dose delays or withdrawal of study drugs in the investigator's choice group. Of the Grade 3-4 adverse events, four were considered serious AEs in the nivolumab group and one was considered a serious AE in the investigator's choice group. All five patients in the nivolumab group were treated with high dose corticosteroids. The AE resolved in all five patients. One patient each experienced Grade 2 diarrhea in the nivolumab group (CA209037-27-37113) and the investigator's choice group (CA209037-46-37593). The study drugs were not interrupted. The patient in the nivolumab group was treated with 40 mg/day of prednisone. On the same day, the patient was diagnosed with disease progression and the patient died after 52 days with the event of colitis ongoing.
Table 30 summarizes the patients with Grade 3 and 4 GI Select AEs.

Table 30: Patients with Grade 3 Gastrointestinal Select Adverse Events (All Treated Population)

Patient ID	Age/ Sex	Treatment	Adverse Event	Grade	Serious	Hosp	Related	Onset (Day)	Duration (days)	Action Taken	Outcome
CA209037-13-37161	65/M	Nivolumab	Diarrhea	3	Y	Y	N	187	5	Dose Not Changed	R
CA209037-15-37264	68/F	Nivolumab	Colitis	3	N	N	Y	72	21	Dose Delayed	R
CA209037-27-37152	80/M	Nivolumab	Colitis	3	Y	Y	Y	29	3	Drug Withdrawn	R
CA209037-39-37563	83/M	Nivolumab	Diarrhea	3	Y	Y	Y	79	11	Dose Delayed	R
CA209037-62-37365	57/M	Nivolumab	Diarrhea	3	Y	Y	N	159	9	Dose Not Changed	R
CA209037-8-37075	65/M	Investigator's Choice	Diarrhea	3	N	N	Y	28	2	Dose Not Changed	R
CA209037-90-37625	52/M	Investigator's Choice	Diarrhea	3	Y	Y	Y	63	8	Dose Not Changed	R

Source: ADAE.xpt
Abbreviations: F, female; Hosp, Hospitalization; M, male; N, no; O, ongoing; R, recovered/resolved; Y, yes.

The median time to onset was 8.3 weeks (range: 0.1 to 37.6 weeks) for patients receiving nivolumab and was 4.1 weeks (range: 0.1 to 16.3 weeks) for patients receiving investigator's choice. For nivolumab, 5 (8.8%) of 57 patients with diarrhea or colitis received corticosteroids for a median duration of 4.7 weeks (range: 2.3 to 38.6 weeks). All five patients received high dose corticosteroids (at least 40 mg prednisone equivalents) and the median initial dose was 1.0 mg/kg (range: 0.5 to 5.3 mg/kg) per day of prednisone equivalent for a median duration of 4.7 weeks (range: 0.6 to 10.3 weeks). Resolution occurred in 52 (91.2%) of 57 patients receiving nivolumab and 17 (94.4%) of 18 patients receiving investigator's choice. The median time to resolution was 1.1 (range 0.4 to 2.1 weeks) and 0.6 weeks (range 0.3 to 2.0 weeks), for patients receiving nivolumab or investigator's choice, respectively. Colitis led to discontinuation of nivolumab in one patient.

Reviewer Comment:

1. *Five patients with Grade 3 colitis or diarrhea and one patient with Grade 2 improved with treatment with corticosteroids.*
2. *The Applicant has established a gastrointestinal AE management algorithm which has been applied across the nivolumab program and remains appropriate for managing gastrointestinal AEs. Refer to the Appendix for the gastrointestinal AE management algorithm.*

Endocrine Select Adverse Events

The Applicant identified endocrine Select AE category included the following subcategories: adrenal disorders, diabetes, pituitary disorders, and thyroid disorders, which occurred 30 days after the last dose of study therapy. The reviewer extended the analysis to up to 100 days after the last dose of study therapy. The total endocrine AEs occurred in 32 (11.9%) patients in the nivolumab group compared to two patients (2%) patients in the investigator's choice group. The most frequently occurring AE (≥ 2% of patients), regardless of causality, were hypothyroidism and hyperthyroidism in the nivolumab group. Drug-related AEs were reported in 21 of 32 patients in the nivolumab group and 1 of 2 patients in the investigator's choice group. Table 31 summarizes the endocrine select adverse events.

Table 31: Summary of Endocrine Adverse Events (All Treated Population)

Adverse Event	**Nivolumab Any grade N=268 n (%)**	**Investigator's choice Any grade N=102 n (%)**
Total Endocrine AE	32 (11.9)	2 (2.0)
Hypothyroidism	20 (7.5)	0
Hyperthyroidism	8 (3.0)	1 (1.0)
Blood Thyroid Stimulating Hormone Increased	4 (1.5)	0
Adrenal Insufficiency	3 (1.1)	1 (1.0)

Thyroiditis*	3 (1.1)	0
Blood Thyroid Stimulating Hormone Decreased	1 (0.4)	0
Thyroxine Free Increased	1 (0.4)	0

Source: ADAE.xpt
*Thyroiditis is a composite term which includes autoimmune thyroiditis

The majority of the endocrine AEs were Grade 1-2 in the nivolumab group. Both patients in the investigator's choice group had Grade 1-2 AEs.

Hypothyroidism, Thyroiditis, and Hyperthyroidism

Hypothyroidism occurred in 20 (7.5%) patients in the nivolumab group and none in the investigator's choice group. All were Grade 1 or Grade 2 in severity. Hypothyroidism developed in two patients with thyroiditis. Nivolumab dose was delayed for one patient (CA209037-90-37547) with Grade 2 hypothyroidism. One patient was hospitalized for a serious Grade 2 hypothyroidism (CA209037-20-37003) considered related to the study drug. The patient recovered after 23 days. The median time to onset was 11.7 weeks (range 3.6 weeks to 50.7 weeks). One patient with hypothyroidism received corticosteroids (less than 40 mg/day prednisone equivalent) for 35 weeks. Seventeen patients received levothyroxine. No patients discontinued nivolumab treatment because of hypothyroidism. Hypothyroidism resolved in nine patients.

Hyperthyroidism occurred in eight (3.0%) patients in the nivolumab group and one (0.9%) patient in the investigator's choice group. Three patients had Grade 2 and five patients had a Grade 1 hyperthyroidism. All the Grade 2 AEs were treated with methimazole or carbimazole and resolved. Three patients with Grade 1 hyperthyroidism resolved without treatment, one resolved after propranolol, and one is ongoing. The median time to onset was 7.1 weeks (range: 0.1 to 14.3 weeks) for patients receiving nivolumab and 3.1 weeks in the patient receiving investigator's choice. None of the patients received corticosteroids. Resolution occurred in 6 (75.0%) of 8 patients receiving nivolumab, with a median time to resolution of 7.0 weeks (range 2.1 to 12.1+ weeks). No patients discontinued nivolumab treatment because of hyperthyroidism.

The reviewer identified three reports of autoimmune thyroiditis (n=1) and thyroiditis (n=2). Narratives for these three cases were requested from the Applicant in an FDA Information Request dated October 31, 2014. All three AEs were Grade 1 in severity. In two patients, the patients also developed hypothyroidism. One patient with thyroiditis was treated with levothyroxine. The two patients who developed hypothyroidism were treated with levothyroxine. Two of the cases resolved, one was ongoing. Nivolumab dose was delayed in one patient. None of the patients were treated with corticosteroids.

Adrenal Insufficiency

Adrenal insufficiency occurred in three (1.1%) patients (CA209037-25-37223, CA209037-27-37089, and CA209037-47-37184) receiving nivolumab and in one (1.0%) patient (CA209037-86-37198) receiving investigator's choice. In the nivolumab group, one patient had Grade 3 and two patients had Grade 2 adrenal insufficiency. One (0.4%) patient in the nivolumab group was hospitalized for a Grade 3 adrenal insufficiency. There were no ≥ Grade 3 AEs in the investigator's choice group. There were no Grade 5 AEs in either group. Nivolumab dose was delayed in all three patients with adrenal insufficiency in the nivolumab group and none in the investigator's choice group. The event was ongoing for one patient at the time of database lock. The Applicant clarified that patient CA209037-27-37089 had a past medical history of adrenal insufficiency adequately controlled with 5 mg/day of prednisone and therefore was not included as an on-going pre-emergent adverse event. After abruptly stopping her prednisone for one week, the patient developed symptoms of adrenal insufficiency, which resolved after initiation of steroids, and therefore identified as treatment emergent in the dataset (Response to 12/2/2014 FDA Information Request).

The median time to onset was 6.1 weeks (range: 2.1 to 15.9 weeks) for patients receiving nivolumab and 3.1 weeks for the patient receiving investigator's choice. For nivolumab, all three patients with adrenal insufficiency received corticosteroids for a median duration of 19.6 weeks (range: 19.1 to 31.9 weeks). One patient received high dose corticosteroids (at least 40 mg prednisone equivalents), with an initial dose of 0.46 mg/kg per day of prednisone equivalent for a 1.6 weeks. Resolution occurred in 2 (66.7%) of three patients receiving nivolumab and did not resolve in the patient receiving investigator's choice. The median time to resolution was 4.7 weeks (range 0.6 to 31.9+ weeks) for patients receiving nivolumab. No patient discontinued nivolumab treatment because of adrenal insufficiency.

Reviewer Comment:

1. *One patient with Grade 2 hypothyroidism and one patient with Grade 3 adrenal insufficiency improved with corticosteroids.*
2. *The Applicant has established an endocrine AE management algorithm which has been applied across the nivolumab program and remains appropriate for managing endocrine AEs. Refer to the Appendix for the endocrine AE management algorithm.*

Hepatic Select Adverse Events and Drug Induced Liver Injury (DILI)

The Applicant identified hepatic Select AE category included the following terms: acute hepatic failure, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, bilirubin conjugated increased, blood bilirubin increased, gamma-glutamyl-transferase (GGT) increased, hepatic enzyme increased, hepatic failure, hepatitis, hepatitis acute, hyperbilirubinemia, liver disorder, liver function test (LFT) abnormal, liver injury, and transaminases increased up to 30 days after the last dose of study therapy. The reviewer also included the terms hepatotoxicity and jaundice which

were not included in the Applicant's analysis and extended the analyses to up to 100 days after the last dose of study drug therapy, leading to the inclusion of an additional three patients in the nivolumab group and one patient in the investigator's choice group. The total hepatic AEs occurred in in 30 patients (11.2%) in the nivolumab group compared to eight (7.8%) patients in the investigator's choice group. The most frequently occurring AEs (≥ 2% of patients), regardless of causality, were AST increased, ALT increased, and blood bilirubin increased in the nivolumab group and AST increased, ALT increased, and GGT increased in the investigator's choice group. Drug-related events were reported in 13 of 30 patients in the nivolumab group and all 8 of 8 patients in the investigator's choice group. Table 32 summarizes the hepatic adverse events.

Table 32: Summary of Hepatic Adverse Events (All Treated Population)

Adverse Event	**Nivolumab Any grade N=268 n (%)**	**Investigator's choice Any grade N=102 n (%)**
Total Hepatic AE	30 (11.2)	8 (7.8)
Aspartate Aminotransferase Increased	23 (8.6)	4 (3.9)
Alanine Aminotransferase Increased	15 (5.6)	3 (2.9)
Blood Bilirubin Increased*	7 (2.6)	0
Gamma-Glutamyltransferase Increased	3 (1.1)	2 (2.0)
Hepatotoxicity	1 (0.4)	0
Liver Function Test Abnormal	1 (0.4)	0
Transaminases Increased	1 (0.4)	1 (1.0)

Source: ADAE.xpt
*blood bilirubin increased is a composite term which includes jaundice

Grade 1 AEs occurred in 17 (6.3%) patients in the nivolumab group compared to five (4.9%) patients in the investigator's choice group. Grade 2 AEs occurred in 4 (1.5%) patients in the nivolumab group compared to one (1.0%) patient in the investigator's choice group. Grade 3-4 AEs occurred in 10 (3.7%) patients in the nivolumab group compared to two (2.0%) patients in the investigator's choice group. Patient CA209037-11-37648 was an additional patient identified in the reviewer's analysis which was not identified in the Applicant's analysis. Two patients in the nivolumab group had a serious AE compared to none in the investigator's choice group. There were no Grade 5 AEs in either group. Nivolumab dose was discontinued in one patient and dose delayed in one patient. Three patients with Grade 3 and one patient with Grade 2 received corticosteroids. Table 33 summarizes the patients with Grade 3-4 hepatic AEs.

Table 33: Patients with Grade 3/4 Hepatic Adverse Events (All Treated Population)

Patient ID	Age/Sex	Treatment	Adverse Event	Grade	Serious	Hosp	Related	Onset (Day)	End (Day)	Action	Outcome
CA209037-105-37439	84/M	Nivolumab	Alanine Aminotransferase Increased	3	N	N	Y	100	104	Dose Delayed	R
		Nivolumab	Aspartate Aminotransferase Increased	3	N	N	Y	97	102	Dose Delayed	R
CA209037-11-37648	42/M	Nivolumab	Blood Bilirubin Increased	3	N	N	N	56	N/A	Dose Not Changed	O
CA209037-13-37161	65/M	Nivolumab	Alanine Aminotransferase Increased	3	N	N	Y	120	121	Dose Delayed	R
			Alanine Aminotransferase Increased	3	Y	Y	Y	170	171	Drug Withdrawn	R
			Liver Function Test Abnormal	3	Y	Y	Y	122	124	Dose Delayed	R
CA209037-1-37214	58/M	Nivolumab	Gamma-Glutamyltransferase Increased	3	N	N	N	15	N/A	Dose Not Changed	O
CA209037-16-37413	70/M	Nivolumab	Alanine Aminotransferase Increased	3	N	N	N	10	17	Dose Not Changed	R
			Alanine Aminotransferase Increased	3	N	N	N	39	40	Dose Not Changed	R
			Alanine Aminotransferase Increased	3	Y	Y	N	6	8	Dose Not Changed	R
			Aspartate Aminotransferase Increased	3	N	N	N	12	17	Dose Not Changed	R
			Aspartate Aminotransferase Increased	3	Y	Y	N	6	8	Dose Not Changed	R
			Blood Bilirubin Increased	3	N	N	N	12	17	Dose Not Changed	R
			Blood Bilirubin Increased	3	N	N	N	37	39	Dose Not Changed	R
CA209037-16-37419	64/M	Nivolumab	Alanine Aminotransferase Increased	3	N	N	N	16	N/A	Dose Not Changed	O
			Aspartate Aminotransferase Increased	4	N	N	N	16	N/A	Dose Not Changed	O

CA209037-20-37098	58/M	Nivolumab	Alanine Aminotransferase Increased	3	N	N	N	142	143	Dose Not Changed	R
			Aspartate Aminotransferase Increased	3	N	N	N	142	142	Dose Not Changed	R
CA209037-41-37354	66/F	Nivolumab	Aspartate Aminotransferase Increased	3	N	N	N	15	N/A	Dose Not Changed	O
CA209037-57-37445	53/F	Investigator's Choice	Alanine Aminotransferase Increased	4	N	N	Y	90	113	Dose Not Changed	R
			Aspartate Aminotransferase Increased	4	N	N	Y	90	113	Dose Not Changed	R
CA209037-63-37270	47/F	Nivolumab	Aspartate Aminotransferase Increased	3	N	N	N	15	N/A	Dose Not Changed	O
CA209037-77-37142		Nivolumab	Gamma-Glutamyltransferase Increased	3	N	N	N	79	88	Dose Not Changed	O
CA209037-90-37625	52/M	Investigator's Choice	Aspartate Aminotransferase Increased	3	N	N	Y	85	N/A	Dose Not Changed	O

Source: ADAE.xpt
Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; F, female; Hosp, Hospitalized; M, male; N/A, not applicable; O, ongoing; R, recovered/resolved.

The median time to onset in the 10 patients was 5.6 weeks (range: 0.9 to 24.3 weeks) for patients receiving nivolumab and was 4.1 weeks (range: 3.1 to 12.9 weeks) for patients receiving investigator's choice. The median time to resolution was 1.1 weeks (range 0.1 to 7.1 weeks) for the nivolumab group and 5.4 weeks (range 3.1 to 19.9 weeks) for the investigator's choice group. Nivolumab was discontinued due to recurrent hepatotoxicity in one patient.

Four patients in the nivolumab group received treatment with corticosteroids: CA209037-105-37439 for Grade 3 elevations in ALT and AST; CA209037-13-37161 for Grade 3 elevation in ALT and Grade 2 elevation in AST; CA209037-16-37413 for Grade 3 elevations in AST, ALT and bilirubin; and CA209037-39-37563 for Grade 2 elevations in AST and ALT. Nivolumab was discontinued in one patient (CA209037-13-37161) and interrupted in one patient (CA209037-105-37439). In both patients, the hepatotoxicity resolved. In the other two patients, the hepatotoxicity was ongoing when the patients were diagnosed with disease progression and subsequently died.

The Applicant identified three patients, CA209037-16-37413, CA209037-16-37419, and CA209037-61-37367 with ALT or AST > 3x ULN and total bilirubin > 2x ULN. The reviewer also conducted an analysis of the laboratory datasets and identified an additional three patients based on the same criteria (CA209037-2-37512, CA209037-39-37154, and CA209037-98-37510) to identify any patients with drug-induced liver injury meeting the criteria for Hy's law. For patient CA209037-61-37367, the reviewer sent a query to the Applicant as it was not clear from the narrative why the patient's death was not attributed to hepatotoxicity due to the 3rd dose of the study drug. The Applicant clarified that a CT scan on Day 30 found progression of metastatic melanoma in the liver, lung, and adrenal gland. On Day 43, the day of the 3rd dose of nivolumab, the patient's liver function test results showed an AST that was greater than 3 x upper limit of normal and a bilirubin that was greater than 2 x ULN. In addition, ALP was markedly elevated, but ALT was only minimally elevated. The Grade 2 increased bilirubin was reported as a non-serious adverse event and considered by the investigator to be related to liver metastases and not related to study therapy. The patient died on Day 58 due to progression of metastatic melanoma.

Reviewer Comments:

1. *There were no Hy's Law cases identified. However, nivolumab has a potential for severe DILI as signaled by the following set of findings:*
    - *An excess of AST or ALT elevations to >3xULN in the nivolumab group (12 patients, 4.5%) compared to the investigator's choice group (2 patients, 2.0%)*
    - *Elevations of AST or ALT to > 5xULN in the nivolumab group (7 patients, 2.6%) compared to one patient (1.0%) in the investigator's choice group.*
    - *Six (2.2%) patients with shift from baseline of total bilirubin to >2xULN in a setting of pure hepatocellular injury, accompanied by an overall increased*

incidence of AST or ALT elevations >3xULN in the nivolumab group compared to one (1.0%) in the investigator's choice group.

2. *Two patients in the nivolumab group had elevations in liver transaminases which improved with corticosteroid therapy.*
3. *For patient CA209037-61-37367, additional details were requested as it was not clear from the narrative that the patient's death could not be attributed to hepatotoxicity due to the third dose of the study drug. The increased AST and bilirubin could be possibly related to nivolumab. The third dose of nivolumab was administered in this patient on Day 43, after progression was found on Day 30.*
4. *The Applicant provided an analysis of hepatotoxicity which was initially submitted to IND115195 in response to an FDA Information Request to identify reports of potential DILI. The analysis included reports from patients treated with nivolumab as single-agent and nivolumab used in combination with ipilimumab, thus confounding the exposure of patients who received nivolumab as single-agent.*
5. *Additional narratives were requested from the Applicant for the cases not included by the Applicant in the initial submission.*
6. *The Applicant has established a hepatic AE management algorithm which has been applied across the nivolumab program and remains appropriate for managing hepatic AEs. Refer to the Appendix for the hepatic AE management algorithm.*
7. *Due to the potential for severe DILI, the reviewer recommends inclusion of routine monitoring of liver functions tests in the label for AST, ALT, total bilirubin, and alkaline phosphatase every two weeks in patients receiving nivolumab, and post-marketing surveillance. Drugs with a predisposition to hepatotoxicity should be used with caution in patients treated with nivolumab.*

Renal Select Adverse Events

The Applicant included the following terms in the renal select AE category: blood creatinine increased, blood urea increased, creatinine renal clearance decreased, hypercreatinemia, nephritis, nephritis allergic, nephritis autoimmune, renal failure, acute renal failure, renal tubular necrosis, tubulointerstitial nephritis, and urine output decreased, selected to encompass those most likely to be reported in a patient with nephritis. The reviewer included an additional term, renal impairment, which was not included in the Applicant's analysis, leading to the inclusion of an additional AE in the nivolumab group. All renal select AEs occurred up 30 days of follow up. Adverse event terms belonging to the renal select AE category occurred in 18 (6.7%) patients in the nivolumab group and four (3.9%) patients in the investigator's choice group. The most frequently occurring AE, regardless of causality, were blood creatinine increased in the nivolumab group and acute renal failure in the investigator's choice group. Trial CA209037 included routine testing for creatinine and blood urea nitrogen (BUN) or

serum urea level every 2 weeks while receiving nivolumab. Table 34 summarizes the renal Select AEs in the All Treated Population.

Table 34: Summary of Renal Select AEs (All Treated Population)

Adverse Event	**Nivolumab Any grade N=268 n (%)**	**Investigator's choice Any grade N=102 N (%)**
Total Renal Select AEs	**18 (6.7)**	**4 (3.9)**
Blood Creatinine Increased	17 (6.3)	1 (1.0)
Blood Urea Increased	1 (0.4)	0
Renal Failure	1 (0.4)	0
Renal Impairment	1 (0.4)	0
Tubulointerstitial Nephritis	1 (0.4)	0
Creatinine Renal Clearance Decreased	0	1 (1.0)
Renal Failure Acute	0	2 (2.0)

Source: ADAE.xpt

Grade 3-4 AEs occurred in five (1.9%) patients in the nivolumab group and one (0.9%) patient in the investigator's choice group. The dose of nivolumab was interrupted in patient CA209037-41-37354 who developed Grade 4 renal failure. Patient CA209037-16-37419 was hospitalized for fever, severe dehydration, acute renal failure, hyperkalemia, hypotension, and atrial fibrillation on Day 15, followed by worsening LFTs. An abdominal ultrasound showed multiple lesions in the liver suspicious for metastatic disease. The patient died on Day 20 due to disease progression. No renal Grade 5 AEs or AEs lead to discontinuation of nivolumab. Table 35 summarizes the patients with Grade 3-4 renal AEs.

Table 35: Summary of Grade 3-4 Renal Adverse Events (All Treated Population)

Patient ID	Age / Sex	Treatment	Adverse Event	Grade	Serious	Hosp	Start (Day)	End (Day)	Action	Related	Outcome
CA209037-10-37443	42/F	Investigator's Choice	Renal Failure Acute	3	Y	Y	32	50	Dose Not Changed	N	R
CA209037-16-37419	64/M	Nivolumab	Blood Creatinine Increased	3	N	N	17	20	Dose Not Changed	N	O
CA209037-20-37003	38/F	Nivolumab	Tubulointerstitial Nephritis	3	Y	Y	108	130	Dose Not Changed	Y	R
CA209037-29-37171	55/M	Nivolumab	Blood Creatinine Increased	3	N	N	79	81	Dose Not Changed	N	R
CA209037-41-37354	66/F	Nivolumab	Renal Failure	4	Y	Y	15	N/A	Drug Interrupted	N	O
CA209037-89-37538	69/F	Nivolumab	Renal Impairment	3	Y	Y	54	55	Dose Not Changed	N	R

Source: ADAE.xpt, Narratives
Abbreviations: F, female; Hosp, hospitalization; M, male; N, no; O, ongoing; R, resolved/recovered; Y, yes

Renal failure, including tubulointerstitial nephritis, and acute renal failure, occurred in 2 (0.7%) of 268 patients receiving nivolumab, including 1 case of Grade 4 renal failure and 1 case of Grade 3 tubulointerstitial nephritis, and 2 (2.0%) of 102 patients receiving investigator's choice, including one case each of Grade 2 and Grade 3 acute renal failure. The median time to onset was 8.8 weeks (range: 2.1 to 15.4 weeks) for patients receiving nivolumab and was 5.3 weeks (range: 4.6 to 6.0 weeks) for patients receiving investigator's choice. For nivolumab, 1 of 2 patients with renal failure received high dose corticosteroids (at least 40 mg prednisone equivalents) and the initial dose of high dose corticosteroids was 1.9 mg/kg per day of prednisone equivalent for 2.7 weeks. Resolution occurred in 1 (50%) of 2 patients receiving nivolumab and in both patients receiving investigator's choice. The median time to resolution was 3.3 weeks (range 0.6+ to 3.3 weeks) or 1.8 weeks (0.9 to 2.7 weeks) for patients receiving nivolumab or investigator's choice, respectively. No patients discontinued nivolumab treatment because of renal failure. One patient with Grade 2 increased creatinine (CA209037-34-37228) considered related by the investigator had the dose of nivolumab delayed and was treated with high-dose corticosteroids.

During the course of Trial CA209003 and prior to the identification of nephritis as an AE belonging to a select AE category, the occurrence of renal SAEs considered by the investigator to be related to study therapy led to a more detailed assessment of this toxicity. Three drug-related SAEs of nephrotoxicity in patients who received single-agent nivolumab were identified as a result of this assessment. Two of these patients were not managed with corticosteroids at the onset. Both of these renal events at least partially resolved following corticosteroid administration. The Applicant subsequently instituted a management guideline for nephrotoxicity which addressed the need for early intervention in patients with elevated serum creatinine along with the need for an extended corticosteroid taper. Safety management guidelines for nephrotoxicity were not in place at the start of Trial CA209003, but were in place before the initiation of Trial CA209037. The guideline for the management of nephrotoxicity was provided to all investigators in version 8 (September 12, 2012) of the Investigator's Brochure. These guidelines were in place at the initiation of Trial CA209037.

Reviewer's Comment:

1. *One patient with Grade 3 tubulointerstitial nephritis improved with corticosteroids.*
2. *The Applicant's nephrotoxicity management algorithm remains appropriate for managing nephrotoxicity. Refer to the Appendix for the nephrotoxicity management algorithm.*

Pulmonary Select Adverse Events

The pulmonary select AE category included the following terms: acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, lung infiltration, and pneumonitis, selected to encompass those most likely to be reported in a patient with pneumonitis.

The Applicant did not include the terms hypoxia and dyspnea because they reflect signs and symptoms rather than a specific underlying etiology. The Applicant states that all events of hypoxia and clinically important events of dyspnea (Grade 1-2 requiring dose modification or Grade 3-4) occurring on or after the first day of dosing were systematically queried to ensure an underlying diagnosis such as pneumonitis, rather than a sign or symptom, was reported if available. Trial CA209037 included routine measurement of oxygen saturation by pulse oximetry every 2 weeks while receiving nivolumab.

The Applicant did not include pneumonia as a term in the pulmonary select AE category because of the high frequency with which it was expected to be reported in the study population, especially to describe infectious etiologies rather than non-infectious pneumonitis. Among the six patients with one or more AEs of pneumonia, four patients received nivolumab (worst grade: 2 Grade 3 events, 1 Grade 4 event, 1 Grade 5 event) and two patients received investigator's choice (2 Grade 2 events), no events of pneumonia were considered drug-related by the investigator.

The Applicant identified eight patients (3.0%) belonging to the pulmonary Select AE category in the nivolumab group and none in the investigator's choice group. The reviewer included an additional patient, patient CA209037-27-37152, in the 100 day follow-up period who received nivolumab (9 patients, 3.4%). Pneumonitis was the most frequently reported term in the nivolumab group (8 patients, 3.0%). Table 36 summarizes the select pulmonary adverse events.

Table 36: Summary of Select Pulmonary Adverse Events (All Treated Population)

Adverse Event	Nivolumab any grade N=268 n (%)	Investigator's choice Grade 3/4 N=102 n (%)
Pneumonitis	8 (3.0)	0
Interstitial Lung Disease	1 (0.4)	0

Source: ADAE.xpt

Three patients had Grade 1 pneumonitis, five patients had Grade 2 pneumonitis, and one patient had Grade 3 pneumonitis. There were no pulmonary Select AEs identified in the investigator's group. There were no Grade 5 AEs. Seven of the nine patients experienced pneumonitis or interstitial lung disease considered by the investigator to be related to nivolumab. The dose of nivolumab was delayed in four patients, three with Grade 2 and one with Grade 1 pneumonitis. In one patient, the pneumonitis event was ongoing at the time of the patient's death which was attributed to disease progression. Table 37 summarizes the patients with pneumonitis or interstitial lung disease.

Table 37: Patients with Pulmonary Adverse Events (All Treated Population)

Patient ID	Age / Sex	Treatment	Adverse Event	Grade	Serious	Hosp	Onset (day)	End (day)	Action	Related	Outcome
CA209037-15-37264	68/F	Nivolumab	Pneumonitis	2	N	N	72	92	Dose Delayed	N	R
CA209037-20-37003	38/F	Nivolumab	Pneumonitis	2	Y	Y	108	130	Dose Not Changed	Y	R
CA209037-27-37152	80/M	Nivolumab	Pneumonitis	3	Y	Y	85	92	Dose Not Changed	Y	R
CA209037-28-37117	78/M	Nivolumab	Pneumonitis	2	N	N	57	98	Dose Delayed	Y	R
CA209037-36-37328	70/M	Nivolumab	Interstitial Lung Disease	2	Y	Y	25	40	Dose Not Changed	Y	R
CA209037-43-37574	45/F	Nivolumab	Pneumonitis	2	N	N	64	85	Dose Delayed	Y	R
CA209037-50-37235	57/F	Nivolumab	Pneumonitis	1	N	N	182	58	Dose Delayed	N	O
CA209037-61-37367	62/M	Nivolumab	Pneumonitis	1	N	N	30	N/A	Dose Not Changed	Y	O
CA209037-90-37547	28/F	Nivolumab	Pneumonitis	1	N	N	58	N/A	Dose Not Changed	Y	O

Source: ADAE.xpt, Narratives
Abbreviations: F, female; Hosp, hospitalization; M, male; N, no; NR, not resolved/not recovered; O, ongoing; R, resolved/recovered; Y, yes

The median time to onset was 9.1 weeks (range: 3.6 to 26.0 weeks). Six (66.7%) of 9 patients with pneumonitis received corticosteroids, one with Grade 3 and five with Grade 2, for a median duration of 4.14 weeks (range: 2.3 to 5.0 weeks). All six patients received high dose corticosteroids (at least 40 mg prednisone equivalents) and the median initial dose was 1.0 mg/kg (range: 0.7 to 2.3 mg/kg) per day of prednisone equivalent for a median duration of 2.7 weeks (range: 0.6 to 4.1 weeks). Resolution occurred in 6 (55.6%) of 9 patients receiving nivolumab with a median time to resolution of 6.0 weeks (range 1.1 to 10.1+ weeks).

Reviewer Comment:

1. *The reviewer noted a discrepancy on whether patient CA209037-27-37152 received corticosteroids for pneumonitis. The dataset did not report corticosteroid treatment, while the narrative reported corticosteroid treatment. The Applicant clarified that the patient did receive corticosteroids (Applicant Response to 12/2/2014 FDA Information Request).*
2. *Six patients, one with Grade 3 and five with Grade 2 improved with corticosteroid treatment.*
3. *Despite the initiation of a pneumonitis management algorithm for early recognition and management of pneumonitis, a fatal AE occurred in another study (Refer to Section 7.3.2). The reviewer recommends a boxed warning in the label for pneumonitis.*

Hypersensitivity/Infusion Reactions

The Applicant analyzed hypersensitivity/infusion reactions and included the following preferred terms: anaphylactic reaction and shock, bronchospasm, hypersensitivity, and infusion-related reaction, selected to encompass those considered most likely to be reported in a subject with hypersensitivity. Adverse event terms in the hypersensitivity/infusion reactions category were reported in eight (3.0%) patients in the nivolumab group and eight (7.8%) patients in the investigator's choice group. Table 38 summarizes the hypersensitivity/infusion reactions.

Table 38: Adverse Events in Hypersensitivity / Infusion Reactions Category (All Treated Population)

Adverse Event	Nivolumab Any Grade N=268 n (%)	Nivolumab Grade 3/4 N=268 n (%)	Investigator's choice Any Grade N=102 n (%)	Investigator's choice Grade 3/4 N=102 n (%)
Infusion Related Reaction	4 (1.5)	1 (0.4)	7 (6.9%)	0
Hypersensitivity	4 (1.5)	0	1 (1.0%)	0

Source: ADAE.xpt

Most of the patients in the nivolumab group and all the patients in the investigator's choice group had Grade 1/2 events. AEs in the hypersensitivity category in 5 out of 8 patients in the nivolumab group and all patients in the investigator's choice group were considered drug-related by the investigator. One patient, CA209037-13-37161, had a Grade 3 infusion related reaction with nivolumab, which occurred on Day 78. No action was taken with study drug. The patient was treated with acetaminophen and IV fluids and the event resolved after 48 hours. No Grade 5 AEs were reported.

Adverse Events of Special Interest

The Applicant identified AEs of special interest based on AEs which may require immunosuppression as part of their management. These included Grades 1-3 uveitis, Grade 3 demyelination, Grade 3 autoimmune neuropathy, and Grade 3 pancreatitis.

Uveitis
Among the three patients with uveitis (CA209037-10-37254 [Grade 3], CA209037-16-37063 [1 Grade 1 and 3 Grade 2 events], and CA209037-50-37002 [Grade 2]), the initial event began between Days 23 and 90, and event duration ranged from 3 days to 29 days. One patient reported multiple events. None of the events were reported as SAEs. All events were considered related to study therapy by the investigator, all events resolved, and none resulted in treatment discontinuation.

Demyelination
One patient (CA209037-59-37230) was hospitalized for drug-related demyelination 47 days after the start of nivolumab treatment. The patient was treated with corticosteroids. The event was ongoing at the time of the patient's death. The autopsy report indicated major pathological findings of metastatic melanoma with extensive spread.

Autoimmune Neuropathy
One patient (CA209037-10-37276) was hospitalized for Grade 3 autoimmune neuropathy 63 days after the start of nivolumab treatment. The patient was treated with corticosteroid and intravenous immunoglobulin and improved.

Pancreatitis
The Applicant identified one patient (CA209037-43-37239) with pancreatitis. The patient was hospitalized for Grade 3 pancreatitis 42 days after the start of nivolumab treatment. She was treated with corticosteroids, the dose of nivolumab was delayed, and pancreatitis improved. The patient was re-hospitalized for pancreatitis and while on a steroid taper, received infliximab. After discontinuation of steroid, the patient had asymptomatic elevations of Grade 3 amylase and Grade 4 lipase. No treatment was administered. The investigator considered all the AEs to be drug-related.

The reviewer included the following terms: increased amylase and increased lipase, and extended the time up to 100 days after the last dose of the study drug. Eleven (4.1%) patients in the nivolumab group and two (2.0%) patients in the investigator's choice group were reported to have pancreatitis, increased amylase, or increased lipase. Table 39 summarizes the pancreatitis observed in the All Treated Population.

Table 39: Summary of Pancreatitis (All Treated Population)

Adverse Event	Nivolumab N=268 N (%)	Investigator's Choice N=102 n (%)
Total events	**11 (4.1)**	**2 (2.0)**
Lipase Increased	9 (3.4)	2 (2.0)
Amylase Increased	6 (2.2)	0
Pancreatitis	2 (0.7)	0

Source: ADAE.xpt

Most of the changes were Grade 1-2. Seven patients had Grade 3 pancreatitis or Grade 3-4 increased amylase or lipase, six (2.2%) in the nivolumab group and one (1.0%) patient in the investigator's choice group. Nivolumab was discontinued for two patients, one patient (CA209037-43-37239) with Grade 3 pancreatitis who required treatment with corticosteroids and infliximab, and one patient (CA209037-77-37142) with Grade 3 lipase elevation who had multiple hospitalizations. Patient CA209037-16-37413 also developed Grade 3 abdominal pain for which nivolumab was discontinued. The patient was found to have pancreatitis and a mass in the pancreas and subsequent disease progression. Nivolumab dose was delayed for three patients with increased lipase. Table 40 summarizes the patients with increased lipase and amylase.

Table 40: Grade 3-4 Pancreatitis (All Treated Population)

Patient ID	Age/ Sex	Treatment	Adverse event	Grade	Serious	Hosp	Related	Action	Onset (day)	Duration (Day)	Outcome
CA209037-16-37413*	70/M	Nivolumab	Lipase Increased	3	N	N	N	Dose Not Changed	42	6	O
CA209037-17-37259	54/M	Nivolumab	Amylase Increased	3	N	N	Y	Dose Delayed	127	15	R
			Amylase Increased	3	N	N	Y	Dose Delayed	149	33	R
			Lipase Increased	3	N	N	Y	Dose Not Changed	113	14	R
			Lipase Increased	4	N	N	Y	Dose Delayed	127	15	R
			Lipase Increased	3	N	N	Y	Dose Delayed	141	8	R
			Lipase Increased	4	N	N	Y	Dose Delayed	149	33	R
			Lipase Increased	3	N	N	Y	Dose Delayed	182	5	R
CA209037-43-37239	71/F	Nivolumab	Pancreatitis	3	Y	Y	Y	Dose Delayed	42	3	R
			Pancreatitis	3	Y	Y	Y	Drug Withdrawn	49	8	R
			Amylase Increased	3	N	N	Y	Dose Delayed	42	9	R
			Amylase Increased	3	N	N	Y	Dose Not Changed	84	43	O
			Lipase Increased	4	N	N	Y	Dose Delayed	42	2	R

			Lipase Increased	3	N	N	Y	Dose Delayed	43	7	R
			Lipase Increased	3	N	N	Y	Dose Not Changed	50	2	R
			Lipase Increased	4	N	N	Y	Dose Delayed	49	2	R
			Lipase Increased	4	N	N	Y	Dose Not Changed	84	43	O
CA209037-60-37322	70/M	Investigator's Choice	Lipase Increased	3	N	N	Y	Dose Delayed	20	9	R
CA209037-71-37105	49/M	Nivolumab	Lipase Increased	3	N	N	N	Dose Not Changed	1	15	R
CA209037-72-37584	50/F	Nivolumab	Amylase Increased	3	N	N	N	Dose Delayed	43	16	R
			Lipase Increased	3	N	N	N	Dose Delayed	43	16	R
CA209037-77-37142	75/M	Nivolumab	Lipase Increased	3	N	N	Y	Drug Withdrawn	104	2	R
			Lipase Increased	3	N	N	Y	Dose Not Changed	113	14	R
			Lipase Increased	4	N	N	Y	Dose Not Changed	127	20	R
			Lipase Increased	3	Y	Y	Y	Dose Not Changed	147	3	R
			Lipase Increased	3	N	N	Y	Dose Not Changed	154	23	R

Source: ADAE.xpt, Case Narratives
Abbreviations: F, female; M, male; N, no; O, ongoing; R, resolved/recovered; Y, yes
*Patient also had abdominal pain and CT showed pancreatitis.

Pancreatitis occurred in 2 (0.7%) of 268 patients receiving nivolumab and none of the patients receiving investigator's choice. One of the 2 cases of pancreatitis cases was Grade 3. The median time to onset was 6.7 weeks (range: 6.0 to 7.4 weeks). One of the 2 patients with pancreatitis received high dose corticosteroids (at least 40 mg prednisone equivalents), with an initial dose of 1.9 mg/kg per day of prednisone equivalent for 4.0 weeks. This patient discontinued nivolumab due to pancreatitis. Both cases of pancreatitis resolved with a median time to resolution of 1.9 weeks (range 1.1 to 2.7 weeks).

Ten (3.7%) of patients treated with nivolumab had either increased amylase or lipase. One patient (CA209037-77-37337) was treated with corticosteroids, which did not resolve (Response to 12/2/2014 FDA Information Request). Six of the 10 patients had resolution of the AE.

Reviewer Comments:

1. *One patient with pancreatitis improved with corticosteroid treatment and discontinuation of nivolumab. One patient with asymptomatic increases in lipase and amylase did not improve with corticosteroids.*
2. *The reviewer recommends the inclusion of pancreatitis in the Warnings and Precautions Section of the label.*

Facial Paresis and Abducens nerve paralysis

One patient (CA209037-101-37645) developed Grade 2 abducens nerve paralysis 26 days after the start of nivolumab treatment. It worsened to Grade 3 after 3 weeks and the patient also developed Grade 3 facial paresis. The patient was treated with corticosteroids. The events were ongoing at the time of the database lock.

The reviewer identified additional AEs of special interest to identify immune-mediated adverse reactions of nivolumab based on AEs observed with other anti-PD-1/PD-L1 approved drugs or investigational agents. These included hypophysitis, hypopituitarism, myasthenia gravis, diabetic ketoacidosis, rhabdomyolysis, transverse myelitis, diabetes mellitus, and hypogonadism. If there were no reports in the BLA submission, the Applicant was requested to conduct an analysis of the AEs across the development program for single-agent nivolumab. The Applicant did not identify any patient with reports of rhabdomyolysis, transverse myelitis, diabetes mellitus, or hypogonadism in the safety database across the development program for single-agent nivolumab (Applicant Response to 11/3/2014 FDA Information Request).

Hypophysitis

In Trial CA209037, three patients had hypophysitis (CA209037-20-37098/Grade 2, CA209037-67-37546/Grade 3, and CA209037-71-37300/Grade 3) at screening, but no treatment-emergent hypophysitis was reported with nivolumab treatment.

The Applicant identified three patients (3/1524, 0.2%) with hypophysitis in the safety database across the development program for single-agent nivolumab. Two patients had Grade 3 events and one was a Grade 2 event. Nivolumab was interrupted in both patients with Grade 3 hypophysitis. All three patients were treated with corticosteroids with steroid taper. Hypophysitis resolved in all three patients. Nivolumab was resumed in the two patients.

Hypopituitarism
There were no reports of hypopituitarism with nivolumab treatment in Trial CA209037.

The Applicant identified one patient (1/1524, 0.07%) with Grade 2 hypopituitarism in the safety database across the development program for single-agent nivolumab. Nivolumab dose was delayed. The patient was treated with hydrocortisone. Hypopituitarism resolved and nivolumab treatment was resumed.

Myasthenia gravis
There were no reports of myasthenia gravis with nivolumab treatment in Trial CA209037.

The Applicant identified one patient (1/1524, 0.07%) with Grade 3 myasthenic syndrome in the safety database across the development program for single-agent nivolumab. Nivolumab was discontinued. The patient was treated with prednisone. The AE resolved.

Diabetic Ketoacidosis
There were no reports of diabetic ketoacidosis with nivolumab treatment in Trial CA209037.

The Applicant identified two patients (2/1524, 0.13%) of Grade 3 diabetic ketoacidosis in the safety database across the development program for single-agent nivolumab. Nivolumab dose was delayed in both patients. The patients were treated with insulin. The AE resolved in both patients and nivolumab was resumed.

Hyperglycemia
Six patients in the nivolumab group and one patient in the investigator's choice group reported hyperglycemia. Out of six patients treated with nivolumab, three patients had Grade 3 events. In the investigator's choice group, the patient had Grade 1 hyperglycemia. In two patients with Grade 3 hyperglycemia, nivolumab dose was delayed. One of the Grade 3 AEs occurred after steroid use and the nivolumab dose was not changed. Hyperglycemia resolved in two patients, and is ongoing in the other patients. The investigator considered hyperglycemia to be drug-related in three patients.

In the 90-day Safety Update, one additional clinically significant AE, Guillain-Barre syndrome was reported outside of Trial CA209037.

Guillain-Barre Syndrome (GBS)
GBS occurred in two patients in Study CA209066. On unblinding, one was found in the nivolumab treatment group and one in the dacarbazine treatment group. The patient in the nivolumab treated group was a 49 year old male who initially developed a Grade 1 gait disturbance after the second dose of nivolumab which persisted until the eighth dose of nivolumab after which he was diagnosed with Grade 3 GBS on Day 100. The patient was treated with IV gamma globulin and corticosteroids with improved symptomology. Nivolumab treatment was discontinued. The AE was ongoing at the time of database lock on Day 146.

Two additional cases occurred in two ongoing randomized studies CA209067 and CA209069. Treatment assignments are unknown as the studies are blinded.

Corticosteroid and Immunosuppressive Treatment

A total of 88 (32.8%) patients in the nivolumab group and 18 (17.6%) patients in the investigator's choice group were treated with corticosteroids for adverse events. In the nivolumab group, 61 (22.8%) patients received corticosteroids for systemic use (intravenous, oral, and intramuscular) and 38 (14.2%) patients received corticosteroids for dermatologic use (topical and transdermal). In the investigator's choice group, 14 (13.7%) patients received corticosteroids for systemic use and five (4.9%) patients received corticosteroids as topical preparations.

One patient had diverticular perforation related to corticosteroid treatment (CA209037-36-37328), which occurred nine days after initiation of corticosteroids for interstitial pneumopathy (methylprednisolone at 120 mg/day, increased to 240 mg/day the next day and continued for 10 days). The area of infectious diverticulitis of the sigmoid colon was drained and the event resolved with the patient discharged with oral antibiotics.

Two patients were treated with infliximab for AE management. One patient (CA209037-43-37239) received one dose of infliximab on Day 105 for Grade 4 lipase which had increased in the setting of a corticosteroid taper used to treat a Grade 3 pancreatitis which lasted from Day 49 to Day 56. The AE resolved on Day 126. The other patient (CA209037-43-37159) received four doses of infliximab from Day 116 through Day 211 for Grade 3 arthritis, in addition to corticosteroids. Arthritis improved to Grade 1 and was ongoing at the time of the database lock.

Two patients were treated with intravenous immunoglobulin (IVIG) for AE management. One patient (CA209037-59-37230) received IVIG 2mg/kg over 5 days from Day 56 in addition to corticosteroids for Grade 3 demyelination which was ongoing at the time of

death from disease progression. The other patient (CA209037-10-37276) received IVIG in addition to corticosteroids for Grade 3 autoimmune neuropathy which resolved.

In Trial CA209003, SAEs occurred in 159 (52%) patients across all tumor types. Drug related SAEs occurred in 42 (13.7%) patients. The most frequently occurring drug related SAE was pneumonitis (7 patients, 2.3%). Of these, pneumonitis occurred in 4 (1.3%) patients was Grade 3-4. In the melanoma group, any Grade SAEs occurred in 51 (47.7%) patients, of which drug related SAEs occurred in 14 (13.1%) patients. Any Grade Select AEs occurred in 208 (68%) patients, of which 140 (45.8%) were drug related. The most frequently occurring drug related categories of Select AEs were skin (25%), gastrointestinal (14%), endocrinopathies (9.5%), and renal (9.5%). The most frequently occurring SAE in the patients receiving 3 mg/kg dose is malignant neoplasm progression (11.1%). Table 41 summarizes the SAEs in ≥5% patients across all doses.

Table 41: Serious and Select Adverse Events Across Doses (Trial CA209003)

Adverse Event	**Nivolumab 0.1 mg/kg N=17 n (%)**	**Nivolumab 0.3 mg/kg N=18 n (%)**	**Nivolumab 1 mg/kg N=86 n (%)**	**Nivolumab 3 mg/kg N=54 n (%)**	**Nivolumab 10 mg/kg N=131 n (%)**
Serious Adverse Events					
Malignant Neoplasm Progression	3 (17.6)	1 (5.6)	12 (14.0)	6 (11.1)	31
Pneumonia	1 (5.9)	0	0	5 (9.3)	5
Pyrexia	1 (5.9)	1 (5.6)	4 (4.7)	3 (5.6)	6
Select Adverse Events					
Skin Adverse Event	4 (23.5)	7 (38.9)	38 (44.2)	25 (46.3)	51 (38.9)
Gastrointestinal Adverse Event	3 (17.6)	4 (22.2)	37 (43.0)	24 (44.4)	44 (33.6)
Endocrine Adverse Event	4 (23.5)	2 (11.1)	11 (12.8)	5 (9.3)	12 (9.2)
Hepatic Adverse Event	1 (5.9)	4 (22.2)	14 (16.3)	5 (9.3)	11 (8.4)
Pulmonary Adverse Event	1 (5.9)	1 (5.6)	7 (8.1)	4 (7.4)	8 (6.1)
Renal Adverse Event	1 (5.9)	2 (11.1)	7 (8.1)	3 (5.6)	16 (12.2)
Hypersensitivity/Infusion Reaction	0	1 (5.6)	4 (4.7)	3 (5.6)	10 (7.6)

Source: ADAE.xpt

Reviewer Comments:

1. *Non-fatal SAEs were higher in the nivolumab group compared to the investigator's choice group. Most immune-mediated adverse events were consistent with the known safety profile of anti-PD1 agents.*
2. *Some adverse events did not occur in Trial CA209037 but occurred across the clinical development program for single-agent nivolumab. These included hypophysitis, hypopituitarism, myasthenic syndrome, and diabetic ketoacidosis.*

3. *Outcomes for several AEs were not provided in the dataset ADAE.xpt and constituted missing data. The Applicant was queried on these missing data. The Applicant stated in their response to FDA Information Request dated October 31, 2014, that the adverse event outcome variable in the dataset ADAE.xpt is collected only for SAEs and not for non-SAEs.*
4. *Age was missing for 45 patients. The Applicant was queried on the missing data. The Applicant clarified that the 45 patients were from Germany and The Netherlands, where full birth dates are not collected due to data privacy laws in the two countries. Thus age is derived based on an imputed birth date for the partial birth dates (Applicant Response to 11/12/2014 FDA Information Request).*
5. *SAEs and Select AEs in patients who received nivolumab 3mg/kg in Trial CA209003 are consistent with those in Trial CA209037.*

7.3.3 Dropouts and/or Discontinuations

AEs, regardless of causality, leading to treatment discontinuation occurred in 25 (9.3%) patients in the nivolumab group and 12 (11.8%) patients in the investigator's choice group. AEs leading to treatment discontinuation of nivolumab that occurred in two or more patients included malignant neoplasm progression in 10 patients and cardiac arrest in two patients. Grade 3-4 AEs leading to treatment discontinuation occurred in 19 (7.1%) patients in the nivolumab group and five (4.9%) patients in the investigator's choice group. Table 42 summarizes the AEs leading to treatment discontinuation.

Table 42: Adverse Events Leading to Treatment Discontinuation (All Treated Population)

Adverse Event	**Nivolumab Any grade N=268 n (%)**	**Nivolumab Grade 3-4 N=268 n (%)**	**Investigator's choice Any grade N=102 n (%)**	**Investigator's choice Grade 3-4 N=102 n (%)**
Total Patients with Event	25 (9.3)	19 (7.1)	12 (11.8)	5 (4.9)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)				
Malignant Neoplasm Progression	10.0 (3.7)	6 (2.2)	2 (2.0)	1 (1.0)
Brain Neoplasm Malignant	1.0 (0.4)	1 (0.4)	0	0
Cardiac Disorders				
Cardiac Arrest	2.0 (0.7)	2 (0.7)	0	0
Gastrointestinal Disorders				
Colitis	1.0 (0.4)	1 (0.4)	0	0
Hematemesis	1.0 (0.4)	1 (0.4)	0	0
Pancreatitis	1.0 (0.4)	1 (0.4)	0	0
General Disorders And Administration Site Conditions				
Asthenia	1.0 (0.4)	1 (0.4)	0	0
Fatigue	1.0 (0.4)	0	2 (2.0)	0

General Physical Health Deterioration	1.0 (0.4)	1 (0.4)	0	0
Infections And Infestations				
Pneumonia	1.0 (0.4)	1 (0.4)	0	0
Investigations				
Alanine Aminotransferase Increased	1.0 (0.4)	1 (0.4)	0	0
Lipase Increased	1.0 (0.4)	1 (0.4)	0	0
Nervous System Disorders				
Autoimmune Neuropathy	1.0 (0.4)	1 (0.4)	0	0
Demyelination	1.0 (0.4)	1 (0.4)	0	0
Hemorrhage Intracranial	1.0 (0.4)	1 (0.4)	0	0
Neuropathy Peripheral	0.0	0	1 (1.0)	0
Peripheral Sensory Neuropathy	0.0	0	1 (1.0)	0
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnea	1.0 (0.4)	0	1 (1.0)	0
Blood And Lymphatic System Disorders				
Anemia	0.0	0	1 (1.0)	0
Thrombocytopenia	0.0	0	1 (1.0)	0
Injury, Poisoning And Procedural Complications				
Infusion Related Reaction	0.0	0	1 (1.0)	0
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	0.0	0	1 (1.0)	0
Hypotension	0.0	0	1 (1.0)	0

Source: ADAE.xpt

The reviewer requested additional details in a FDA Information Request dated September 17, 2014, and the Applicant clarified the details in the following patients:

The reason for patient CA209037-40-37323 discontinuing the study is stated to be "subject withdrew consent." The narrative describes that the patient developed Grade 3 herpes zoster on Day 25 and Grade 3 post-herpetic neuralgia on Day 44. The investigator considered both serious adverse events to be related to study therapy. The patient withdrew consent on Day 46. The reviewer sent a query to the Applicant as it was not clear why the patient was not counted among the patients who discontinued due to drug toxicity as it appeared that the reason for the withdrawal is the study drug toxicity. The Applicant clarified that in this follow-up with the site, the investigator has confirmed they will update the data accordingly including counting this patient as having discontinued study drug due to toxicity (Response to 9/17/2014 FDA Information Request).

For patient CA209037-35-37047, the reviewer sent a query to the Applicant as it was not clear why the patient was not counted among the patients who discontinued due to study drug toxicity as it appeared that the "subject request to discontinue study treatment" is related to study drug toxicity. The Applicant clarified that the investigator discussed with the medical monitor a preference to discontinue the study drug therapy (discontinued on (b) (6) given the patient had already had an ongoing

durable response since (b) (6), but was experiencing some low grade adverse events that did not require discontinuation per protocol. The Applicant states that the treatment was discontinued in the context of durable response with low-grade AEs, rather than as the result of unmanageable study drug toxicity in isolation. The AEs were non-serious Grade 2 myalgia and Grade 2 pain considered by the investigator to be related to study therapy (Response to 9/17/2014 FDA Information Request).

The reviewer conducted further analyses of cardiac AEs.

Cardiac Events

Cardiac AEs occurred in 29 (10.9) patients in the nivolumab group and two (2.0%) patients in the investigator's choice group. The most frequently occurring cardiac AE in the nivolumab group were arrhythmias including tachycardia (n=8), atrial fibrillation (n=5), palpitations (n=5), sinus tachycardia (n=4), atrial flutter (n=2), arrhythmia (n=1), supraventricular tachycardia (n=1), ventricular arrhythmia (n=1), and ventricular fibrillation (n=1). Table 43 summarizes the cardiac AEs.

Table 43: Cardiac Adverse Events (All Treated Population)

Adverse Event	Nivolumab Any grade N=268 n (%)	Nivolumab Grade 3-4 N=268 n (%)	Investigator's choice Any grade N=102 n (%)	Investigator's choice Grade 3-4 N=102 n (%)
Total Cardiac Event	**29 (10.9)**	**9 (3.4)**	**2 (2.0)**	**1 (0.4)**
Tachycardia	8 (3.0)	0	0	0
Atrial Fibrillation	5 (1.9)	3 (1.1)	0	0
Palpitations	5 (1.9)	0	1 (0.4)	0
Sinus Tachycardia	4 (1.5)	1 (0.4)	0	0
Cardiac Arrest	3 (1.1)	3 (1.1)	0	0
Atrial Flutter	2 (0.7)	1 (0.4)	0	0
Bradycardia	2 (0.7)	0	0	0
Supraventricular Tachycardia	1 (0.4)	1 (1.1)	0	0
Ventricular Arrhythmia	1 (0.4)	1 (1.1)	0	0
Ventricular Fibrillation	1 (0.4)	1 (1.1)	0	0
Arrhythmia	1 (0.4)	0	0	0
Sinus Bradycardia	1 (0.4)	0	0	0
Myocardial Infarction	0	0	1 (0.4)	1 (1.0)

Source: ADAE.xpt

Grade 3-4 AEs occurred in 11 (45.1%) patients in the nivolumab group compared to one (0.4%) in the investigator's choice group. The most frequent Grade 3-4 AEs were arrhythmias, which occurred in eight (3.0%) patients in the nivolumab group, and included atrial fibrillation (n=3), atrial flutter (n=1), sinus tachycardia (n=1), supraventricular tachycardia(n=1), ventricular arrhythmia (n=1), ventricular fibrillation

(n=1). No arrhythmias occurred in the investigator's choice group. Out of 12 arrhythmia reports, six were considered serious by the investigator, nine were hospitalized, and one AE was considered related to nivolumab. The dose of nivolumab was not changed for arrhythmias but the drug was discontinued for two patients with cardiac arrest. One patient (CA209037-16-37413) had Grade 3 atrial fibrillation after 30 days after the first dose of nivolumab and again had multiple hospitalizations; however he had a history of atrial fibrillation. It is unknown whether the atrial fibrillation was ongoing at the time of the patient's death on Day 65 which was due to disease progression. Another patient (CA209037-16-37419) had Grade 3 atrial fibrillation after five days after the first dose of nivolumab; however he had a history of atrial fibrillation and was diagnosed with disease progression to the stomach and died on Day 20. Both these AEs were not considered by the investigator to be related to the study drug. Patient CA209037-50-37008 was hospitalized 11 days after the second dose of nivolumab for Grade 3 ventricular arrhythmia which was considered by the investigator to be related to study drug. No action was taken with regard to the study therapy. On Day 29, the event of ventricular arrhythmia resolved. By the time of database lock, the patient had received an additional 29 doses of nivolumab without further occurrence of ventricular arrhythmias. Treatment with study therapy, amiodarone, and fludrocortisone was continuing.

Two patients had cardiac arrest. One patient (CA209037-50-37189) was a patient with pre-treatment tachycardia in whom cardiac arrest occurred on the day the patient died of disease progression. The investigator confirmed that the patient had rapid progression of his liver metastasis. Refer to Section 7.3.1 for details on this patient. The other patient (CA209037-67-37526) was found to have progressive disease. The reviewer requested additional details in a FDA Information Request dated September 17, 2014, and the Applicant clarified the following: The reason for the patient CA209037-67-37526 discontinuing the study is described as "other" and "adverse event unrelated to study drug" in the dataset ADSL. However the reason in the narrative is "AE leading to discontinuation." The narrative also states that Grade 4 cardiac arrest occurred on Day 59, two days after the fifth dose of nivolumab and that "Study therapy was discontinued due to the event of cardiac arrest…" It was not clear why the patient is not counted among the patients who discontinued due to drug toxicity as it appears that the reason for discontinuation is due to the cardiac arrest. The reviewer sent a query to the Applicant for an explanation on why the patient is not counted among the patients who discontinued due to drug toxicity as it appears that the reason for discontinuation is due to the cardiac arrest. The Applicant clarified that the investigator confirmed that the Grade 4 cardiac event was considered unrelated to study drug and was considered likely related to an unconfirmed pulmonary embolism unrelated to study drug. The patient was also found to have progressive disease (Applicant Response to 9/17/2014 FDA Information Request). Given the overall clinical picture, the investigator decided to discontinue study drug. The reason for discontinuation of study drug was entered as cardiac arrest not related to study drug. The investigator considered the cardiac arrest to be secondary to an unconfirmed pulmonary embolism unrelated to study drug.

Therefore, study drug toxicity was not entered as the reason for treatment discontinuation.

Two patients in the nivolumab group had Grade 5 adverse events, cardio-respiratory failure (CA209037-24-37631), and cardiac failure (CA209037-9-37286). Refer to Section 7.3.1 for details on these two patients. Grade 4 or Grade 5 AEs did not occur in the investigator's choice group. Table 44 summarizes the patients with cardiac AEs.

Table 44: Patients with Grade 3-4 Cardiac Events (All Treated Population)

Patient ID	Age/ Sex	Treatment	Adverse Event	Grade	Serious	Hosp	Start Day (Day)	End Day (Day)	Action	Related	Outcome
CA209037-16-37413	70/M	Nivolumab	Atrial Fibrillation	3	Y	Y	31	32	Dose Not Changed	N	R
			Atrial Fibrillation	3	Y	Y	54	59	Dose Not Changed	N	R
			Sinus Tachycardia	3	Y	Y	31	32	Dose Not Changed	N	R
			Sinus Tachycardia	3	Y	Y	42	48	Dose Not Changed	N	R
CA209037-16-37419	64/M	Nivolumab	Atrial Fibrillation	3	Y	Y	6	12	Dose Not Changed	N	R
			Atrial Fibrillation	4	Y	Y	15	20	Dose Not Changed	N	O
CA209037-17-37259	54/M	Nivolumab	Cardiac Arrest	4	Y	Y	132	132	Dose Not Changed	N	R
			Ventricular Fibrillation	4	N	N	132	132	Dose Not Changed	N	R
CA209037-50-37008	55/M	Nivolumab	Ventricular Arrhythmia	3	Y	Y	26	29	Dose Not Changed	Y	R
CA209037-50-37189	63/M	Nivolumab	Cardiac Arrest	4	Y	N	26	26	Drug Withdrawn	N	O
CA209037-62-37251	33/F	Nivolumab	Supraventricular Tachycardia	3	N	N	30	30	Dose Not Changed	N	R
CA209037-67-37526	64/M	Nivolumab	Cardiac Arrest	4	Y	Y	59	61	Drug Withdrawn	N	O
CA209037-71-37105	49/M	Nivolumab	Atrial Fibrillation	3	Y	Y	82	86	Dose Not Changed	N	R
CA209037-86-37198	83/M	Investigator's Choice	Myocardial Infarction	3	Y	Y	97	101	Dose Not Changed	N	R

CA209037-87-37487	61/M	Nivolumab	Atrial Flutter	3	N	N	55	57	Dose Not Changed	N	R
			Atrial Flutter	3	Y	Y	83	85	Dose Not Changed	N	R
CA209037-9-37286	54/M	Nivolumab	Cardiac Failure	4	Y	Y	50	71	Dose Not Changed	N	O

Source: ADAE.xpt, Case Narratives
Abbreviations: F, female; M, male; N, no; O, ongoing; R, resolved/recovered; Y, yes.

Reviewer Comment:
Cardiac AEs occurred more frequently in the nivolumab group compared to the investigator's choice group. Most were confounded by underlying medical history of atrial fibrillation, and underlying metastatic melanoma with disease progression including sequelae thereof.

In the 90-day Safety Update, three additional patients in the nivolumab group discontinued due to study drug toxicity. Patient CA029037-5-37588 had 'elevated liver enzymes', patient CA209037-9-37091 had 'abnormal liver function test results', and patient CA209037-77-37142 had 'high lipase'.

In Trial CA209003, drug related AEs leading to discontinuation occurred in 32 (10.5%) patients. Grade 3-4 drug related events occurred in 14 (4.6%) patients. Pneumonitis was the most common treatment related AE leading to discontinuation, which occurred in eight (2.6%) patients. In the melanoma group, discontinuations occurred due to pneumonitis (n=2), colitis (n=2, one Grade 3-4), and hepatitis (n=1, Grade 3-4). In the 3mg/kg cohort, discontinuations occurred due to pneumonitis (n=1), and Grade 3-4 hepatitis (n=1).

7.3.4 Significant Adverse Events

Grade 3-4 Adverse Events

Grade 3 and 4 adverse events which occurred up to 100 days occurred in 113 (42.2%) patients in the nivolumab group compared to 51 (50%) patients in the investigator's choice group. The most frequent (≥2%) Grade 3-4 AEs in the nivolumab group were malignant neoplasm progression (21 patients, 7.8%), anemia (13 patients, 4.9%), abdominal pain (nine patients, 3.4%), hyponatremia (seven patients, 2.6%), and six patients each with vomiting, general physical health deterioration, increased aspartate aminotransferase, and increased lipase (2.2%). Table 45 summarizes the Grade 3 and 4 AEs.

Table 45: Grade 3 and 4 Adverse Events ≥1% (All Treated Population)

Adverse Event	Nivolumab N=268			Investigator's Choice N=102		
	Grade 3 n (%)	Grade 4 n (%))	Grade 3-4 n (%))	Grade 3 n (%)	Grade 4 n (%)	Grade 3-4 n (%)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)						
Malignant Neoplasm Progression	12 (4.5)	9 (3.4)	21 (7.8)	2 (2.0)	0	2 (2.0)
Metastatic Malignant Melanoma	5 (1.9)	0	5 (1.9)	0	0	0
Blood And Lymphatic System Disorders						
Anemia	13 (4.9)	0	13 (4.9)	8 (7.8)	1 (1.0)	9 (8.8)
Leukocytosis	4 (1.5)	0	4 (1.5)	0	0	0
Gastrointestinal Disorders						
Abdominal Pain	9 (3.4)	0	9 (3.4)	1 (1.0)	0	1 (1.0)
Vomiting	6 (2.2)	0	6 (2.2)	2 (2.0)	0	2 (2.0)
Diarrhea	3 (1.1)	0	3 (1.1)	2 (2.0)	0	2 (2.0)
Nausea	3 (1.1)	0	3 (1.1)	2 (2.0)	0	2 (2.0)
Metabolism And Nutrition Disorders						
Hyponatremia	6 (2.2)	1 (0.4)	7 (2.6)	0	0	0
Dehydration	3 (1.1)	0	3 (1.1)	0	0	0
Hyperglycemia	3 (1.1)	0	3 (1.1)	0	0	0
Hyperkalemia	3 (1.1)	0	3 (1.1)	0	0	0
General Disorders And Administration Site Conditions						
General Physical Health Deterioration	3 (1.1)	3 (1.1)	6 (2.2)	0	0	0
Fatigue	4 (1.5)	0	4 (1.5)	6 (5.9)	0	6 (5.9)
Pain	3 (1.1)	0	3 (1.1)	2 (2.0)	0	2 (2.0)
Investigations						
Aspartate Aminotransferase Increased	5 (1.9)	1 (0.4)	6 (2.2)	1 (1.0)	1 (1.0)	2 (2.0)
Lipase Increased	3 (1.1)	3 (1.1)	6 (2.2)	1 (1.0)	0	1 (1.0)
Alanine Aminotransferase Increased	5 (1.9)	0	5 (1.9)	0	1 (1.0)	1 (1.0)

Blood Alkaline Phosphatase Increased	4 (1.5)	0	4 (1.5)	0	0	0
Amylase Increased	3 (1.1)	0	3 (1.1)	0	0	0
Musculoskeletal And Connective Tissue Disorders						
Back Pain	5 (1.9)	0	5 (1.9)	1 (1.0)	0	1 (1.0)
Infections And Infestations						
Pneumonia	3 (1.1)	1 (0.4)	4 (1.5)	0	0	0
Sepsis	1 (0.4)	3 (1.1)	4 (1.5)	0	0	0
Urinary Tract Infection	4 (1.5)	0	4 (1.5)	0	0	0
Vascular Disorders						
Hypotension	2 (0.7)	2 (0.7)	4 (1.5)	1 (1.0)	0	1 (1.0)
Cardiac Disorders						
Atrial Fibrillation	2 (0.7)	1 (0.4)	3 (1.1)	0	0	0
Cardiac Arrest	0	3 (1.1)	3 (1.1)	0	0	0
Respiratory, Thoracic And Mediastinal Disorders						
Dyspnea	3 (1.1)	0	3 (1.1)	2 (2.0)	0	2 (2.0)

Source: ADAE.xpt

In Trial CA209003, Grade 3-4 AEs occurred in 17% patients across all tumor types. The most frequent Grade 3-4 AE in the patients receiving nivolumab 3 mg/kg were pneumonia and lymphopenia (four patients each, 7.4%).

Dose Delays

Per protocol CA209037, nivolumab dose reductions and escalations were not permitted. Dose delays due to AEs occurred in 69 (25.7%) patients in the nivolumab group and 31 (30.4 %) patients in the investigator's choice group. The most frequent AEs (≥1%) leading to dose delays of nivolumab were dyspnea (7 patients, 2.6%), four patients each with increased lipase, increased amylase, and pneumonitis (1.5%), and three patients each with abdominal pain, adrenal insufficiency, arthralgia, and headache (1.1%). Table 46 summarizes the adverse events leading to dose delays.

Table 46: Adverse Events Leading to Dose Delays (All Treated Population)

Adverse event	Nivolumab Any grade N=268 n (%)	Nivolumab Grade 3-4 N=268 n (%)	Investigator's choice Any grade N=102 n (%)	Investigator's choice Grade 3-4 N=102 n (%)
Respiratory, Thoracic And Mediastinal Disorders				
Dyspnea	7 (2.6)	1 (0.4%)	0	0
Pneumonitis	4 (1.5)	0	0	0
Cough	2 (0.7)	0	0	0
Hypoxia	2 (0.7)	1(0.4%)	0	0
Investigations				
Amylase Increased	4 (1.5)	3 (1.1)	0	0
Lipase Increased	4 (1.5)	3 (1.1)	1 (1.0)	1 (1.0)
Alanine Aminotransferase Increased	2 (0.7)	2 (0.7)	0	0
Aspartate Aminotransferase Increased	2 (0.7)	1 (0.4)	0	0
Blood Creatinine Increased	2 (0.7)	0	0	0
Endocrine Disorders				
Adrenal Insufficiency	3 (1.1)	1 (0.4)	0	0
Gastrointestinal Disorders				
Abdominal Pain	3 (1.1)	3 (1.1)	0	0
Diarrhea	2 (0.7)	1 (0.4)	0	0
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	3 (1.1)	0	0	0
Nervous System Disorders				
Headache	3 (1.1)	1 (0.4)	0	0
General Disorders And Administration Site Conditions				
Asthenia	2 (0.7)	0	0	0
Infections And Infestations				
Cellulitis	2 (0.7)	2 (0.7)	1 (1.0)	0
Pneumonia	2 (0.7)	2 (0.7)	1 (1.0)	0

Urinary Tract Infection	2 (0.7)	2 (0.7)	0	0
Metabolism And Nutrition Disorders				
Hyperglycemia	2 (0.7)	2 (0.7)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)				
Malignant Neoplasm Progression	2 (0.7)	1 (0.4)	0	0

Source: ADAE.xpt

The reviewer conducted an additional analysis of pancreatitis. Refer to Section 7.3.2 for details in Trial CA209037.

In Trial CA209003, two patients, one with melanoma and the other with non-squamous NSCLC, treated with 1 mg/kg and 3 mg/kg respectively were reported to have pancreatitis and increased amylase. The pancreatitis was considered to be related to nivolumab by the investigator. Nivolumab was interrupted for pancreatitis and withdrawn for increased amylase.

Reviewer Comment:
A higher frequency of Grade 3-4 AEs occurred in the nivolumab group compared to the investigator's choice group, leading to a higher frequency of discontinuation from study treatment.

7.3.5 Submission Specific Primary Safety Concerns

Patients Treated Beyond Progression

The Applicant provided AE tables for 37 patients in the ORR population treated beyond progression in response to the FDA Information Request dated October 31, 2014. Grade 5 AEs occurred in six patients, five of whom had malignant neoplasm progression. One patient had cardiac failure (CA209037-9-37286). Details are provided in Section 7.3.1. The frequency of Grade 3 or 4 AEs and SAEs were higher in the patients treated beyond progression. SAEs in at least one patient included rash, adrenal insufficiency, hypothyroidism, erysipelas, urinary tract infection, postoperative ileus, splenic hematoma, small intestinal obstruction, dehydration, convulsion, tubulointerstitial nephritis, pulmonary embolism, pneumonitis, atrial fibrillation, and anemia. Grade 3-4 AEs occurring in two or more patients included anemia, hyponatremia, back pain, abdominal pain and increased lipase. Table 47 summarizes the Grade 3-4 AEs in the patients treated post progression.

Table 47: Adverse Events in Patients Treated Post Progression

Adverse Event	Nivolumab Any Grade N=37 n (%)	Nivolumab Grade 3-4 N=37 n (%)
Anemia	11 (29.7)	5 (13.5)
Hyponatremia	5 (13.5)	4 (10.8)

Back Pain	9 (24.3)	3 (8.1)
Metastatic Malignant Melanoma	3 (8.1)	3 (8.1)
Abdominal Pain	6 (16.2)	2 (5.4)
Lipase Increased	3 (8.1)	2 (5.4)
Asthenia	5 (13.5)	1 (2.7)
Rash	4 (10.8)	1 (2.7)
Blood Alkaline Phosphatase Increased	3 (8.1)	1 (2.7)
Urinary Tract Infection	3 (8.1)	1 (2.7)
Dehydration	2 (5.4)	1 (2.7)
Hypertension	2 (5.4)	1 (2.7)
Lymphadenopathy	2 (5.4)	1 (2.7)
Spinal Pain	2 (5.4)	1 (2.7)
Adrenal Insufficiency	1 (2.7)	1 (2.7)
Amylase Increased	1 (2.7)	1 (2.7)
Atrial Fibrillation	1 (2.7)	1 (2.7)
Cancer Pain	1 (2.7)	1 (2.7)
Cardiac Arrest	1 (2.7)	1 (2.7)
Erysipelas	1 (2.7)	1 (2.7)
Hemorrhagic Anemia	1 (2.7)	1 (2.7)
Malignant Neoplasm Progression	1 (2.7)	1 (2.7)
Metastases To Adrenals	1 (2.7)	1 (2.7)
Metastases To Central Nervous System	1 (2.7)	1 (2.7)
Metastatic Pain	1 (2.7)	1 (2.7)
Monoplegia	1 (2.7)	1 (2.7)
Pathological Fracture	1 (2.7)	1 (2.7)
Postoperative Ileus	1 (2.7)	1 (2.7)
Pulmonary Embolism	1 (2.7)	1 (2.7)
Small Intestinal Obstruction	1 (2.7)	1 (2.7)
Splenic Hematoma	1 (2.7)	1 (2.7)
Splenic Lesion	1 (2.7)	1 (2.7)
Supraventricular Tachycardia	1 (2.7)	1 (2.7)
Tubulointerstitial Nephritis	1 (2.7)	1 (2.7)
Tumor Pain	1 (2.7)	1 (2.7)
Ventricular Fibrillation	1 (2.7)	1 (2.7)

Source: ADAE.xpt, ADRS.xpt

Reviewer's Comments:

1. *SAEs and Grade 3-4 AEs occurred in a higher proportion of patients treated post progression compared to the All Treated population.*
2. *There were no case definitions for the identification of immune-mediated AEs in the protocol and specific immune-mediated AEs were not identified in the protocol.*

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequent (≥ 10% in either treatment group) MedDRA System Organ Classes (SOCs) in both groups in CA209037 occurring up to 30 days are shown in Table 48. The analysis up to 100 days was similar to the 30 day analysis.

Table 48: Summary of System Organ Class (All Treated Population)

System Organ Class	Nivolumab N=268 n (%)	Investigator's choice N=102 n (%)
General Disorders And Administration Site Conditions	173 (64.6)	62 (60.8)
Gastrointestinal Disorders	151 (56.3)	69 (67.6)
Skin And Subcutaneous Tissue Disorders	117 (43.7)	40 (39.2)
Musculoskeletal And Connective Tissue Disorders	104 (38.8)	42 (41.2)
Respiratory, Thoracic And Mediastinal Disorders	97 (36.2)	27 (26.5)
Infections And Infestations	90 (33.6)	26 (25.5)
Nervous System Disorders	83 (31)	40 (39.2)
Metabolism And Nutrition Disorders	79 (29.5)	24 (23.5)
Investigations	74 (27.6)	29 (28.4)
Blood And Lymphatic System Disorders	56 (20.9)	47 (46.1)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	56 (20.9)	7 (6.9)
Psychiatric Disorders	45 (16.8)	9 (8.8)
Vascular Disorders	39 (14.6)	13 (12.7)
Endocrine Disorders	28 (10.4)	2 (2)
Cardiac Disorders	27 (10.1)	1 (1)
Eye Disorders	26 (9.7)	3 (2.9)
Injury, Poisoning And Procedural Complications	26 (9.7)	12 (11.8)

Source: ADAE.xpt

Treatment emergent adverse events (TEAEs) occurred in most patients in both the groups. Twelve patients in the nivolumab group did not have any AEs reported in the ADAE.xpt dataset for the clinical study report database lock. The most common AEs (≥ 20%) in the nivolumab group compared to the investigator's choice group were fatigue (38.8% vs. 43.1%), nausea (23.9% vs. 42.2%) and diarrhea (20.1% vs. 16.7%). Table 49 lists TEAEs occurring at ≥ 5% incidence in the nivolumab group.

Table 49: Treatment Emergent Adverse Events ≥ 5% (All Treated Population)

	Nivolumab N=268			Investigator's Choice N=102		
System Organ Class Adverse Event	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)	All Grades n (%)	Grade 3-4 n (%)	Grade 5 n (%)

General Disorders And Administration Site Conditions						
Fatigue	104 (38.8)	4 (1.5)	0	44 (43.1)	5 (4.9)	0
Pyrexia	35 (13.1)	0	0	10 (9.8)	1 (1.0)	0
Edema Peripheral	28 (10.4)	0	0	5 (4.9)	0	0
Asthenia	26 (9.7)	2 (0.7)	0	8 (7.8)	1 (1.0)	0
Pain	21 (7.8)	3 (1.1)	0	4 (3.9)	1 (1.0)	0
Gastrointestinal Disorders						
Nausea	64 (23.9)	3 (1.1)	0	43 (42.2)	2 (2.0)	0
Diarrhea	54 (20.1)	2 (0.7)	0	17 (16.7)	2 (2.0)	0
Vomiting	37 (13.8)	6 (2.2)	0	24 (23.5)	2 (2.0)	0
Constipation	35 (13.1)	2 (0.7)	0	20 (19.6)	1 (1.0)	0
Abdominal Pain	30 (11.2)	9 (3.4)	0	7 (6.9)	0	0
Skin And Subcutaneous Tissue Disorders						
Pruritus	51 (19.0)	0	0	4 (3.9)	0	0
Rash	32 (11.9)	1 (0.4)	0	5 (4.9)	0	0
Dry Skin	17 (6.3)	0	0	1 (1.0)	0	0
Rash Maculo-Papular	15 (5.6)	0	0	2 (2.0)	0	0
Vitiligo	14 (5.2)	0	0	0	0	0
Blood And Lymphatic System Disorders						
Anemia	42 (15.7)	12 (4.5)	0	28 (27.5)	8 (7.8)	0
Respiratory, Thoracic And Mediastinal Disorders						
Cough	41 (15.3)	0	0	5 (4.9)	0	0
Dyspnea	41 (15.3)	3 (1.1)	0	15 (14.7)	2 (2.0)	0
Metabolism And Nutrition Disorders						
Decreased Appetite	39 (14.6)	0	0	18 (17.6)	0	0
Hypernatremia	15 (5.6)	7 (2.6)	0	1 (1.0)	0	0
Musculoskeletal And Connective Tissue Disorders						
Arthralgia	35 (13.1)	0	0	15 (14.7)	2 (2.0)	0
Back Pain	25 (9.3)	4 (1.5)	0	2 (2.0)	1 (1.0)	0
Musculoskeletal Pain	20 (7.5)	0	0	3 (2.9)	0	0
Musculoskeletal Pain	20 (7.5)	0	0	3 (2.9)	0	0
Pain In Extremity	18 (6.7)	0	0	9 (8.8)	2 (2.0)	0
Myalgia	15 (5.6)	0	0	8 (7.8)	0	0
Nervous System Disorders						
Headache	30 (11.2)	2 (0.7)	0	11 (10.8)	0	0
Dizziness	18 (6.7)	0	0	5 (4.9)	0	0
Investigations						
Aspartate Aminotransferase Increased	23 (8.6)	6 (2.2)	0	3 (2.9)	0	0
Blood Creatinine Increased	17 (6.3)	2 (0.7)	0	1 (1.0)	0	0
Weight Decreased	16 (6.0)	0	0	5 (4.9)	0	0
Blood Alkaline Phosphatase Increased	15 (5.6)	4 (1.5)	0	2 (2.0)	0	0
Alanine Aminotransferase Increased	14 (5.2)	5 (1.9)	0	2 (2.0)	0	0
Psychiatric Disorders						
Insomnia	23 (8.6)	1 (0.4)	0	5 (4.9)	0	0
Endocrine Disorders						

Hypothyroidism	19 (7.1)	0	0	0	0	0
Infections And Infestations						
Nasopharyngitis	19 (7.1)	0	0	1 (1.0)	0	0
Urinary Tract Infection	14 (5.2)	4 (1.5)	0	4 (3.9)	0	0
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)						
Malignant Neoplasm Progression	14 (5.2)	11 (4.1)	16 (6.0)	2 (2.0)	2 (2.0)	2 (2.0)

Source: ADAE.xpt

The review of safety evaluated additional potential toxicities of study drug therapy through analyses of the incidence of AEs based on hierarchical composites of MedDRA preferred terms (i.e., high level terms) and a hierarchical composites of MedDRA high-level terms (i.e., high-level group terms) in each treatment group. The common high level terms are asthenic conditions (61%), nausea and vomiting symptoms (34%), and musculoskeletal and connective tissue pain and discomfort (30%). Table 50 summarizes the incidence of high level terms occurring in ≥ 10% of the nivolumab group compared to the investigator's choice group.

Table 50: Treatment Emergent Adverse Events (≥ 10%) by High Level Term (All Treated Population)

High Level Term	**Nivolumab N=268 n (%)**	**Investigator's choice N=102 N (%)**
Asthenic Conditions	165 (61.6)	71 (69.6)
Nausea And Vomiting Symptoms	90 (33.6)	56 (54.9)
Musculoskeletal And Connective Tissue Pain And Discomfort	79 (29.5)	27 (26.5)
Pruritus Nec	70 (26.1)	5 (4.9)
Appetite Disorders	69 (25.7)	27 (26.5)
Gastrointestinal Atonic And Hypomotility Disorders Nec	69 (25.7)	31 (30.4)
Gastrointestinal And Abdominal Pains (Excl Oral And Throat)	66 (24.6)	22 (21.6)
Coughing And Associated Symptoms	63 (23.5)	12 (11.8)
Diarrhea (Excl Infective)	61 (22.8)	17 (16.7)
Neoplasms Malignant Site Unspecified Nec	61 (22.8)	14 (13.7)
Breathing Abnormalities	55 (20.5)	19 (18.6)
Joint Related Signs And Symptoms	55 (20.5)	20 (19.6)
Pain And Discomfort Nec	55 (20.5)	14 (13.7)
Anemias Nec	52 (19.4)	33 (32.4)
Rashes, Eruptions And Exanthems Nec	47 (17.5)	7 (6.9)
Febrile Disorders	39 (14.6)	11 (10.8)
Headaches Nec	39 (14.6)	13 (12.7)
Edema Nec	38 (14.2)	7 (6.9)
Upper Respiratory Tract Infections	37 (13.8)	5 (4.9)
Disturbances In Initiating And Maintaining Sleep	33 (12.3)	9 (8.8)
Dermal And Epidermal Conditions Nec	32 (11.9)	5 (4.9)
Liver Function Analyses	30 (11.2)	8 (7.8)

Source: AE.xpt, ADSL.xpt

Table 51 summarizes the incidence of high level group terms occurring in the nivolumab group compared to the investigator's choice group. The common high level group terms occurring in the nivolumab group are general system disorders (71%), gastrointestinal signs and symptoms (52%), and epidermal and dermal conditions (44%).

Table 51: Treatment Emergent Adverse Events (≥ 10%) by High Level Group Term (All Treated Population)

High Level Group Term	Nivolumab N=268 n (%)	Investigator's choice N=102 n (%)
General System Disorders Nec	189 (70.5)	77 (75.5)
Gastrointestinal Signs And Symptoms	140 (52.2)	67 (65.7)
Epidermal And Dermal Conditions	118 (44.0)	19 (18.6)
Gastrointestinal Motility And Defecation Conditions	109 (40.7)	40 (39.2)
Respiratory Disorders Nec	102 (38.1)	31 (30.4)
Musculoskeletal And Connective Tissue Disorders Nec	86 (32.1)	30 (29.4)
Infections - Pathogen Unspecified	79 (29.5)	22 (21.6)
Appetite And General Nutritional Disorders	70 (26.1)	28 (27.5)
Miscellaneous And Site Unspecified Neoplasms Malignant And Unspecified	61 (22.8)	14 (13.7)
Joint Disorders	57 (21.3)	21 (20.6)
Anemias Nonhemolytic And Marrow Depression	55 (20.5)	34 (33.3)
Neurological Disorders Nec	55 (20.5)	25 (24.5)
Headaches	40 (14.9)	13 (12.7)
Body Temperature Conditions	39 (14.6)	11 (10.8)
Muscle Disorders	39 (14.6)	15 (14.7)
Skin Appendage Conditions	36 (13.4)	36 (35.3)
Electrolyte And Fluid Balance Conditions	33 (12.3)	6 (5.9)
Sleep Disorders And Disturbances	33 (12.3)	9 (8.8)
Hepatobiliary Investigations	30 (11.2)	8 (7.8)
Thyroid Gland Disorders	30 (11.2)	2 (2.0)

Source: AE.xpt, ADSL.xpt

The clinical review also included safety analyses of Trial CA209037 using a narrow-based Standardized MedDRA Queries (SMQ). Table 52 summarizes the incidence of narrow based SMQ terms in the two groups.

Table 52: Analysis of Narrow Based Standardized MedDRA Queries (All Treated Population)

SMQ NAME	Nivolumab N=268 n (%)	Investigator's choice N=102

		n (%)
Gastrointestinal nonspecific inflammation and dysfunctional conditions (SMQ)	169 (63.1)	78 (76.5)
Gastrointestinal nonspecific symptoms and therapeutic procedures (SMQ)	165 (61.6)	77 (75.5)
Malignancies (SMQ)	91 (34.0)	19 (18.6)
Malignant or unspecified tumors (SMQ)	74 (27.6)	16 (15.7)
Malignant tumors (SMQ)	73 (27.2)	16 (15.7)
Hypersensitivity (SMQ)	69 (25.7)	12 (11.8)
Noninfectious diarrhea (SMQ)	62 (23.1)	17 (16.7)
Hemodynamic edema, effusions and fluid overload (SMQ)	58 (21.6)	17 (16.7)
Hemorrhage terms (excl laboratory terms) (SMQ)	37 (13.8)	14 (13.7)
Hemorrhages (SMQ)	37 (13.8)	14 (13.7)
Drug related hepatic disorders - comprehensive search (SMQ)	36 (13.4)	9 (8.8)
Hepatic disorders (SMQ)	36 (13.4)	9 (8.8)
Liver related investigations, signs and symptoms (SMQ)	35 (13.1)	8 (7.8)
Oropharyngeal disorders (SMQ)	31 (11.6)	8 (7.8)
Thyroid dysfunction (SMQ)	29 (10.8)	2 (2.0)

Source: AE.xpt, ADSL.xpt

In Trial CA209003, any grade, treatment related AEs occurred in 75% and Grade 3-4 AEs occurred in 17% of patients across all tumor types.

Reviewer Comments:

1. *Although per protocol, nonserious AEs were collected up to 100 days, the common AE analyses was conducted up to 30 days due to the potential for being confounded by subsequent therapies.*
2. *Although agreed to in the pre-BLA meeting, the Applicant did not provide a SMQ flag in the AE datasets. The reviewer conducted an analysis of narrow-based SMQ terms.*
3. *Common AEs occurred more frequently in the nivolumab group compared to the investigator's choice group.*

7.4.2 Laboratory Findings

Abnormalities in hematology tests were primarily Grade 1 to 2 in severity. Hematologic abnormalities (lymphocytes, hemoglobin, platelet count, leukocytes, and absolute neutrophil count) occurred less frequently in the nivolumab group compared with the investigator's choice group. Abnormalities in liver function tests were primarily Grade 1 to 2 in severity. Grade 3-4 increases in liver function tests (ALP, ALT, AST, and total bilirubin) occurred more frequently in the nivolumab group compared to investigator's choice group. Abnormalities in renal function occurred more frequently in the nivolumab group compared to the investigator's choice group. The most common (≥20%) laboratory abnormalities (all grades) in the nivolumab group were increased alkaline phosphatase (37%) and AST (31%) compared to 30% and 14% in the investigator's

choice group. Grade 3 or 4 alkaline phosphatase and AST occurred in 3% and 2% patients in the nivolumab group and 1% each in the investigator's choice group. Table 53 summarizes the laboratory abnormalities.

Table 53: Treatment Emergent Laboratory Abnormalities (All Treated Population)

Laboratory Parameter	Nivolumab N=268		Investigator's choice N=102	
	Any grade n (%)	Nivolumab Grade 3-4 n (%)	Any grade n (%)	Investigator's choice Grade 3-4 n (%)
Hematology				
Lymphocytes (absolute) (x10*9 c/L)	199 (74.3)	23 (8.6)	77 (75.5)	19 (18.6)
Hemoglobin (g/L)	185 (69.0)	17 (6.3)	82 (80.4)	9 (8.8)
Platelet Count ($x10^9$ c/L)	34 (12.7)	0	44 (43.1)	9 (8.8)
Leukocytes ($x10^9$ c/L)	29 (10.8)	1 (0.4)	56 (54.9)	14 (13.7)
Absolute Neutrophil Count (x10*9 c/L)	22 (8.2)	3 (1.1)	45 (44.1)	21 (20.6)
Liver Function Tests				
Alkaline Phosphatase (ALP) (U/L)	99 (36.9)	7 (2.6)	31 (30.4)	1 (1.0)
Aspartate Aminotransferase (AST) (U/L)	83 (31.0)	6 (2.2)	14 (13.7)	1 (1.0)
Alanine Aminotransferase (ALT) (U/L)	53 (19.8)	4 (1.5)	8 (7.8)	0
Bilirubin, Total (umol/L)	26 (9.7)	1 (0.4)	1 (1.0)	0
Renal Function				
Creatinine (umol/L)	42 (15.7)	2 (0.7)	13 (12.7)	0

Source: ADAE.xpt

Thyroid Function Tests

A higher proportion of patients with TSH levels ≤ upper limit of normal (ULN) at baseline experienced TSH elevations (> ULN) in the nivolumab group (21.2%) compared to the investigator's choice group (5.5%). A higher proportion of patients in the nivolumab group had at least one on-study elevated TSH and one T3 or T4 < lower limit of normal (LLN) (11.0%) compared to the investigator's choice group (1.1%).

The frequency of patients with TSH ≥ LLN at baseline that experienced low TSH levels (< LLN) was similar between the nivolumab and investigator's choice groups. The frequency of patients with at least one on-study low TSH and one free T3 or T4 > ULN was also similar between the two groups. Table 54 summarizes the TSH measurements.

Table 54: Abnormal Thyroid Tests (All Treated Population)

Thyroid Function Tests	Nivolumab N=236	Investigator's Choice N=91
Elevated TSH > ULN	59 (25.0)	14 (15.4)
Elevated TSH > ULN With TSH ≤ ULN At Baseline	50 (21.2)	5 (5.5)
Elevated TSH > ULN		
With At Least One Ft3/Ft4 Test Value < LLN	26 (11.0)	1 (1.1)
With All Other Ft3/Ft4 Test Values ≥ LLN	24 (10.2)	7 (7.7)
With Ft3/Ft4 Test Missing	9 (3.8)	6 (6.6)
Low TSH < LLN	31 (13.1)	12 (13.2)
Low TSH < LLN With TSH ≥ LLN At Baseline	20 (8.5)	8 (8.8)
Low TSH < LLN		
With At Least One Ft3/Ft4 Test Value > ULN	10 (4.2)	3 (3.3)
With All Other Ft3/Ft4 Test Values ≤ ULN	16 (6.8)	9 (9.9)
With Ft3/Ft4 Test Missing	5 (2.1)	0

Source: ADLB.xpt

Electrolyte Abnormalities

The Applicant did not provide an analysis of the electrolyte abnormalities observed in Trial CA209037, which was provided in response to the September 17, 2014 FDA Information Request.

The frequency of electrolyte laboratory parameters worsened from baseline in the nivolumab group compared to the investigator's choice group. Hyperkalemia and hyponatremia worsened from baseline in more patients (≥ 5% difference) in the nivolumab group than the investigator's choice group. Hypercalcemia, hypocalcemia, hypokalemia, hypermagnesemia, and hypernatremia worsened from baseline in a similar proportion of patients (< 5% difference) in each group. Hypomagnesemia worsened from baseline in more patients (≥ 5% difference) on the investigator's choice group than the nivolumab group. Table 55 summarizes the electrolyte abnormalities.

Table 55: Electrolyte Abnormalities (All Treated Population)

Laboratory Test	Nivolumab			Investigator's Choice		
	N	Grade 1-4 n (%)	Grade 3-4 n (%)	N	Grade 1-4 n (%)	Grade 3-4 n (%)
Hypercalcemia	254	14 (5.5)	0	94	1 (1.1)	0
Hypocalcemia	254	38 (15.0)	2 (0.8)	94	12 (12.8)	1 (1.1)
Hyperkalemia	256	39 (15.2)	5 (2.0)	95	6 (6.3)	0
Hypokalemia	256	21 (8.2)	2 (0.8)	95	7 (7.4)	0
Hypermagnesemia	251	12 (4.8)	4 (1.6)	92	2 (2.2)	0
Hypomagnesemia	251	18 (7.2)	0	92	16 (17.4)	1 (1.1)
Hypernatremia	256	11 (4.3)	0	95	1 (1.1)	0
Hyponatremia	256	63 (24.6)	13 (5.1)	95	17 (17.9)	1 (1.1)

Source: Applicant Response to 9/17/2014 FDA Information Request.

7.4.3 Vital Signs

Based on analyses of mean value and mean change from baseline at each cycle, no clinically meaningful differences in systolic blood pressure, diastolic blood pressure, heart rate, or temperature were observed during the course of treatment with either study group.

7.4.4 Electrocardiograms (ECGs)

Safety ECGs and/or triplicate ECGs were not collected in Study CA209037. Therefore, no QT prolongation effect can be assessed for patients in Study CA209037. The FDA Clinical Pharmacology agreed with the proposed assessment of QTc prolongation potential in Study CA209010 at the Type C Written Response only minutes dated July 10, 2013.

The QT substudy (N=146) was conducted in Study CA209010 to determine the QT prolongation potential of nivolumab. Nivolumab within the range of doses studied up to 10 mg/kg did not meaningfully affect the QTc interval. There was no dose response for QTcF, ΔQTcF or change from baseline in heart rate, PR interval, or QRS interval after either the first dose or the seventh dose. No patient had a QTcF interval > 470 msec or a ΔQTcF > 45 msec. In addition, there was no relationship between QTcF change from baseline and nivolumab serum concentration. After examination of events of seizure/convulsion, syncope/presyncope, QTc prolongation, and tachycardia, no event was determined to be associated with an abnormal ECG finding potentially related to proarrhythmia.

Refer to Clinical Pharmacology Review for additional details.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application.

7.4.6 Immunogenicity

Characterization of immunogenicity was an exploratory objective of Trial CA209037. Blood samples were collected and evaluated for the presence of antibodies to nivolumab (anti-drug antibodies [ADA]) using a validated ECL immunoassay in human serum. The presence of neutralizing antibodies was also evaluated in ADA positive samples using a validated cell-based, functional assay. Analyses were conducted on immunogenicity evaluable patients, a total of 180 treated patients with available data.

During treatment, anti-nivolumab ADAs were not detected in 168/180 (93.3%) patients with evaluable ADA data at baseline and post-baseline, and were detected in 12/180 (6.7%) patients with evaluable ADA data at baseline and post baseline, of whom two

(1.1%) patients were persistent positive. Additionally, out of 12 ADA positive patients, two patients (one persistent positive, one other positive) each had one ADA positive sample with neutralizing antibodies detected.

Out of the 12 patients, one patient, CA209037-61-37367, developed Grade 1 pruritus on Day 6, five days after the first dose of nivolumab was administered, and Grade 1 urticaria on Day 7, and considered by the investigator to be related to study drug. No action was taken with regard to study drug, and no specific treatment was provided. On Day 58, the patient died due to malignant neoplasm progression. The events of Grade 1 pruritis and urticaria were ongoing at the time of his death. The duration of the pruritis and urticaria events was 53+ and 52+ days, respectively. Another patient, CA209037-69-37207, developed Grade 1 fever and chills, which occurred on Day 1, the day of the first dose of nivolumab administered. It was considered by the investigator to be related to study drug. The events were treated with acetaminophen. No action was taken with regard to study drug. The fever and chills resolved on the next day. The duration of the events was 2 days. The patient received 19 additional doses of nivolumab without recurrence of fever or chills.

Refer to the Clinical Pharmacology Review for additional details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The Clinical Pharmacology Review did not identify significant covariates influencing nivolumab PK or exposure-response relationships for safety.

Refer to Clinical Pharmacology Review for details.

7.5.2 Time Dependency for Adverse Events

Refer to Section 7.3 for analyses of time dependency for AEs.

7.5.3 Drug-Demographic Interactions

Subgroup analyses based on race was not performed as the study population was almost entirely (>97%) Caucasian. Subgroup analyses based on age and gender is shown below.

Age was missing for 45 patients. The Applicant clarified to the November 12, 2014 FDA Information Request query, that the 45 patients were from Germany and The Netherlands, where full birth dates are not collected due to data privacy laws in the two

countries, but have a partial birth date. Thus for the partial birth dates, age is derived based on an imputed birth date variable in the dataset.

All AEs and SAEs appear to be similar across ages < 65 years and age ≥ 65 years. AEs leading to discontinuation were higher in patients ≥ 65 years of age, and Grade 3-4 AEs were higher in patients < 65 years of age. Select AEs did not show a consistent pattern in the two age groups. The safety profile on nivolumab across age is summarized in Table 56.

Table 56: Adverse Events by Age (All Treated Population)

	Nivolumab N=268				**Investigator's Choice N=102**			
	<65 years N=175 n (%)	**≥65 to < 75 years N=54 n (%)**	**≥75 years N=39 n (%)**	**≥65 years N=93 n (%)**	**<65 years N=60 n (%)**	**≥65 to < 75 years N=29 n (%)**	**≥75 years N=13 n (%)**	**≥65 years N=42 n (%)**
All Adverse Events	165 (94.3)	52 (96.3)	38 (97.4)	90 (96.8)	56 (93.3)	26 (89.7)	13 (100.0)	39 (92.9)
All Serious Adverse Events	76 (43.4)	25 (46.3)	17 (43.6)	42 (45.2)	12 (20.0)	6 (20.7)	4 (30.8)	10 (23.8)
All Adverse Events leading to Discontinuation	14 (8.0)	5 (9.3)	6 (15.4)	11 (11.8)	7 (11.7)	3 (10.3)	2 (15.4)	5 (11.9)
Grade 3-4 Adverse Events	65 (37.1)	15 (27.8)	12 (30.8)	27 (29.0)	27 (45.0)	11 (37.9)	6 (46.2)	17 (40.5)
Select Adverse Events								
Endocrine	26 (14.9)	2 (3.7)	4 (10.3)	6 (6.5)	1 (1.7)	0	1 (7.7)	1 (2.4)
Gastrointestinal	34 (19.4)	10 (18.5)	11 (28.2)	21 (22.6)	10 (16.7)	6 (20.7)	1 (7.7)	7 (16.7)
Hepatic	12 (6.9)	11 (20.4)	5 (12.8)	16 (17.2)	4 (6.7)	2 (6.9)	1 (7.7)	3 (7.1)
Pulmonary	5 (2.9)	2 (3.7)	1 (2.6)	3 (3.2)	0	0	0	0
Renal	9 (5.1)	5 (9.3)	4 (10.3)	9 (9.7)	3 (5.0)	1 (3.4)	0	1 (2.4)
Skin	53 (30.3)	25 (46.3)	18 (46.2)	43 (46.2)	10 (16.7)	3 (10.3)	2 (15.4)	5 (11.9)

Hypersensitivity/Infusion Reactions	4 (2.3)	2 (3.7)	2 (5.1)	4 (4.3)	6 (10.0)	1 (3.4)	1 (7.7)	2 (4.8)

Source: Applicant Response to 11/12/2014 FDA Information Request.

All AEs, SAEs, and Grade 3-4 AEs appear to be similar across both genders. AEs leading to discontinuation were higher in males. Select AEs did not show a consistent pattern in the two gender groups. The safety profile on nivolumab across genders is summarized in Table 57.

Table 57: Adverse Events by Gender (All Treated Population)

	Nivolumab N=268		**Investigator's Choice N=102**	
	Male N=170 n (%)	**Female N=93 n (%)**	**Male N=70 n (%)**	**Female N=32 n (%)**
All Adverse Events	168 (96.0)	87 (93.5)	66 (94.3)	29 (90.6)
All Serious Adverse Events	84 (48.0)	34 (36.6)	16 (22.9)	6 (18.8)
All Adverse Events leading to Discontinuation	20 (11.4)	5 (5.4)	10 (14.3)	2 (6.3)
Grade 3-4 Adverse Events	59 (33.7)	33 (35.5)	31 (44.3)	13 (40.6)
Select Adverse Events				
Endocrine	17 (9.7)	15 (16.1)	1 (1.4)	1 (3.1)
Gastrointestinal	33 (18.9)	22 (23.7)	10 (14.3)	7 (21.9)
Hepatic	21 (12.0)	7 (7.5)	4 (5.7)	3 (9.4)
Pulmonary	3 (1.7)	5 (5.4)	0	0
Renal	13 (7.4)	5 (5.4)	2 (2.9)	2 (6.3)
Skin	65 (37.1)	31 (33.3)	11 (15.7)	4 (12.5)
Hypersensitivity/Infusion Reactions	7 (4.0)	1 (1.1)	6 (8.6)	2 (6.3)

Source: Applicant Response to 11/12/2014 FDA Information Request.

7.5.4 Drug-Disease Interactions

Refer to FDA Clinical Pharmacology Review.

7.5.5 Drug-Drug Interactions

Refer to FDA Clinical Pharmacology Review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not conduct carcinogenicity studies.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant conducted a reproductive toxicity study in the cynomolgus monkey. The FDA Pharmacology/Toxicology reviewers recommend classification of nivolumab as Pregnancy Category D.

Refer to the FDA Pharmacology/Toxicology Review for details.

7.6.3 Pediatrics and Assessment of Effects on Growth

Nivolumab has not been studied in a pediatric population. The Applicant is requesting waiver of pediatric studies based on an exemption from PREA requirements as nivolumab was granted orphan drug designation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant states that in clinical trials conducted by the Japanese company Ono Pharmaceutical Co. Ltd., patients received up to 20 mg/kg nivolumab without apparent toxic effect. Doses greater than 20 mg/kg should be considered an overdose. There is no evidence that suggests a risk for dependence on nivolumab. No cases of withdrawal symptoms were reported during human clinical trials.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

Nivolumab was submitted for marketing authorization in Japan by Ono Pharmaceutical and was approved for treatment of unresectable melanoma on July 4, 2014. The approved dose of nivolumab in Japan is 2 mg/kg administered as an intravenous infusion Q3W.

The Applicant provided spontaneous postmarketing cases from Japan reported for nivolumab from July 4, 2014 to July 29, 2014 of two individual safety reports which consisted of one malignant neoplasm progression with fatal outcome, and a nonserious event of infusion-related reaction with unknown outcome. The Applicant states that no new safety concerns were identified based on the postmarketing reports.

9 Appendices

9.1 Literature Review/References

Aldesleukin (Proleukin), Prometheus Laboratories, Inc., USPI 07/2012, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/103293s5130lbl.pdf

Dabrafenib (Tafinlar), GlaxoSmithKline, USPI 01/2014, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202806s002lbl.pdf

Ipilimumab (Yervoy), Bristol-Myers Squibb Company, USPI 10/2012, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125377s033lbl.pdf

Nivolumab Investigator's Brochure. 2014. Bristol-Myers Squibb, Princeton, NJ 08543.

Pembrolizumab (Keytruda), Merck & Co., Inc. USPI 09/2014, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125514lbl.pdf

Trametinib (Mekinist), GlaxoSmithKline, USPI 01/2014, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/204114s001lbl.pdf

Vemurafenib (Zelboraf), Genentech USA, Inc., USPI 03/2014, Drugs@FDA: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202429s004lbl.pdf

9.2 Labeling Recommendations

Refer to the package insert of Opdivo.

9.3 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drug Advisory Committee (ODAC) for this application as the safety profile is acceptable based on the indicated population, 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 with unresectable or metastatic melanoma who have progressed after treatment with ipilimumab, and if BRAF V600 positive, a BRAF inhibitor; and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. For a general risk benefit discussion, the Division was unable to consult

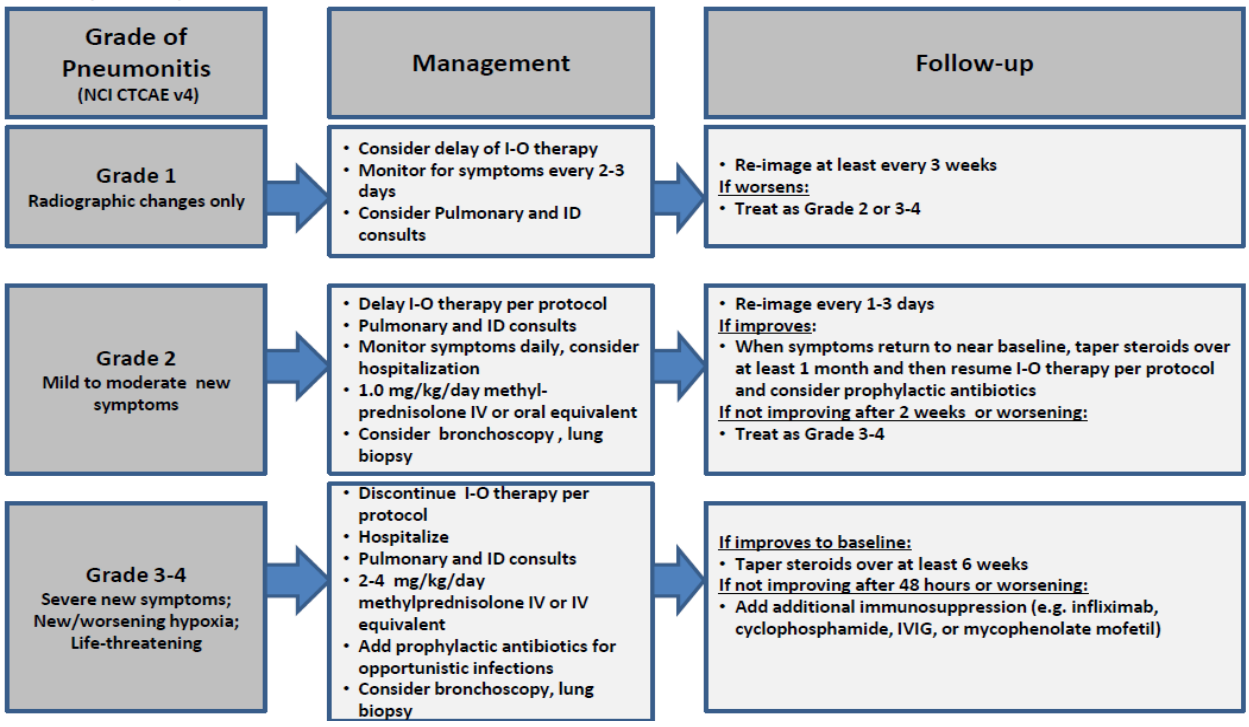
any consultants due to conflicts of interest, including multiple interests with competing products in advanced melanoma and stock holdings.

9.4 Adverse Event Management Algorithms

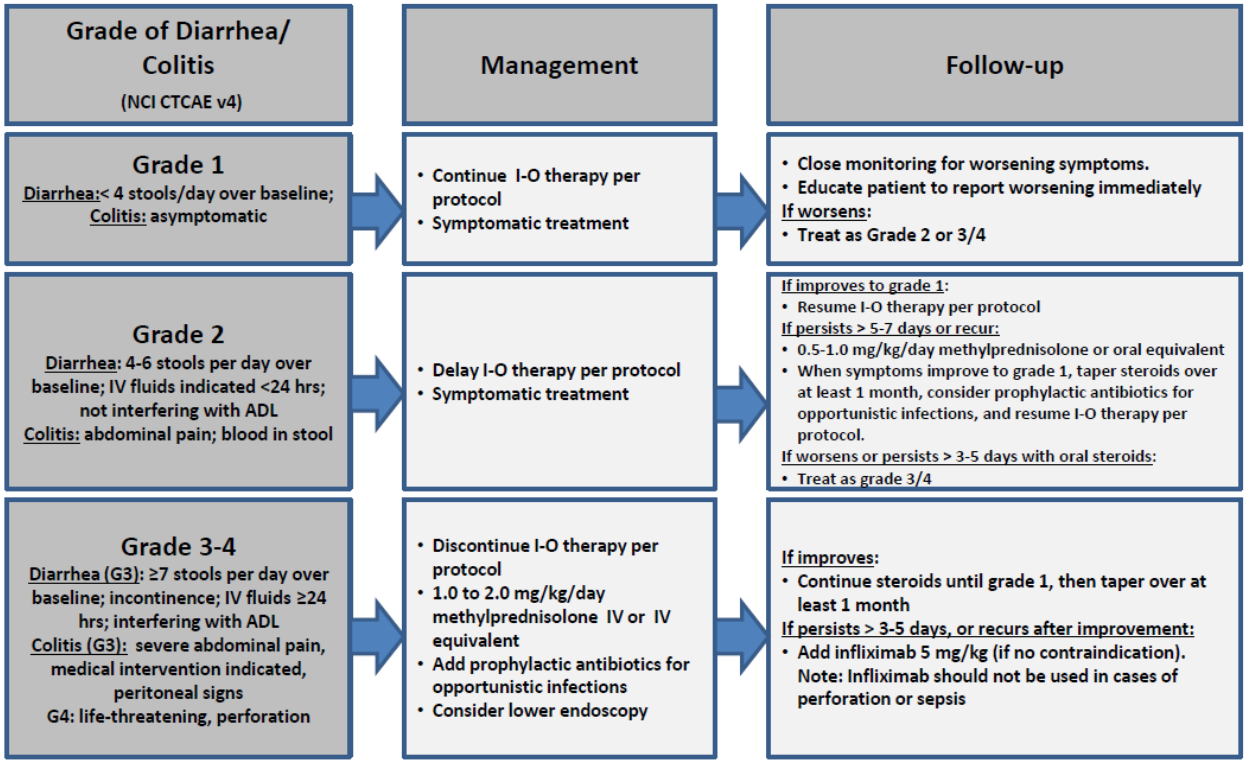
The protocol referred to the Investigator's Brochure for the algorithms for the management of immune-mediated adverse events. The source for the management algorithms reproduced below are from the Investigator's Brochure for nivolumab/BMS-936558/MDX1106, version 13, dated July 21, 2014.

For all adverse events, rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immune-oncology (I-O) therapy. Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

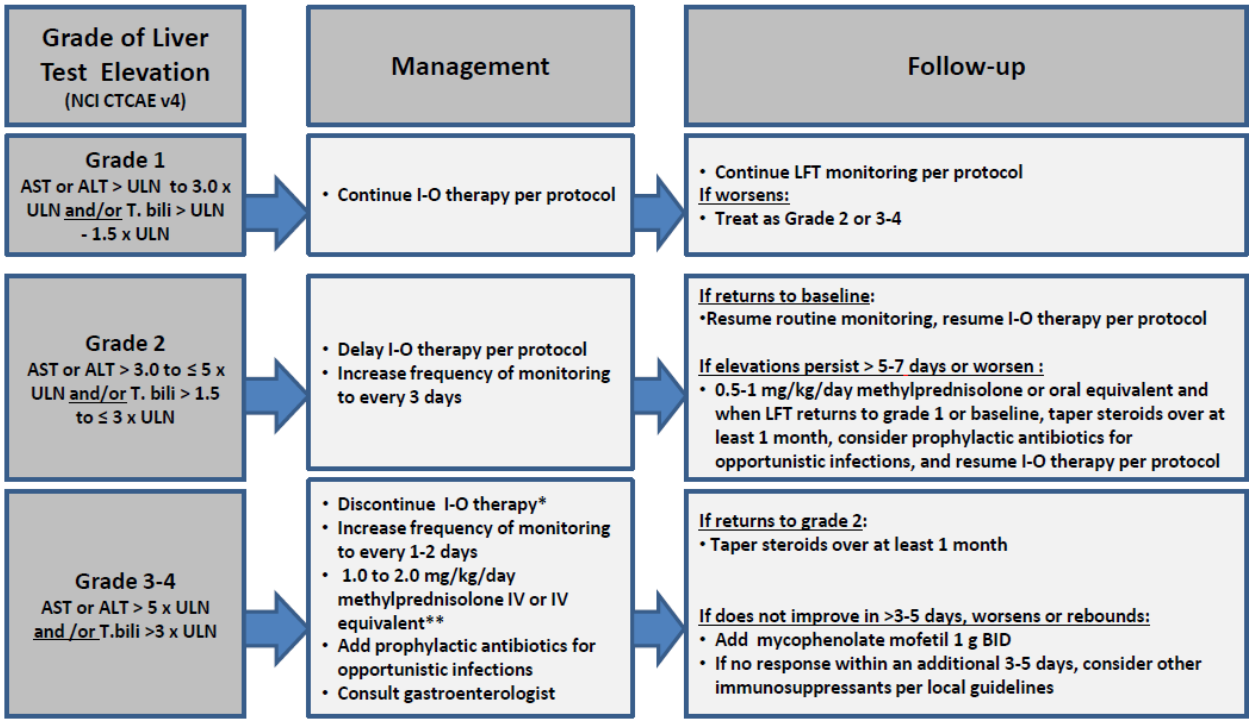
Pulmonary Adverse Events Management Algorithm



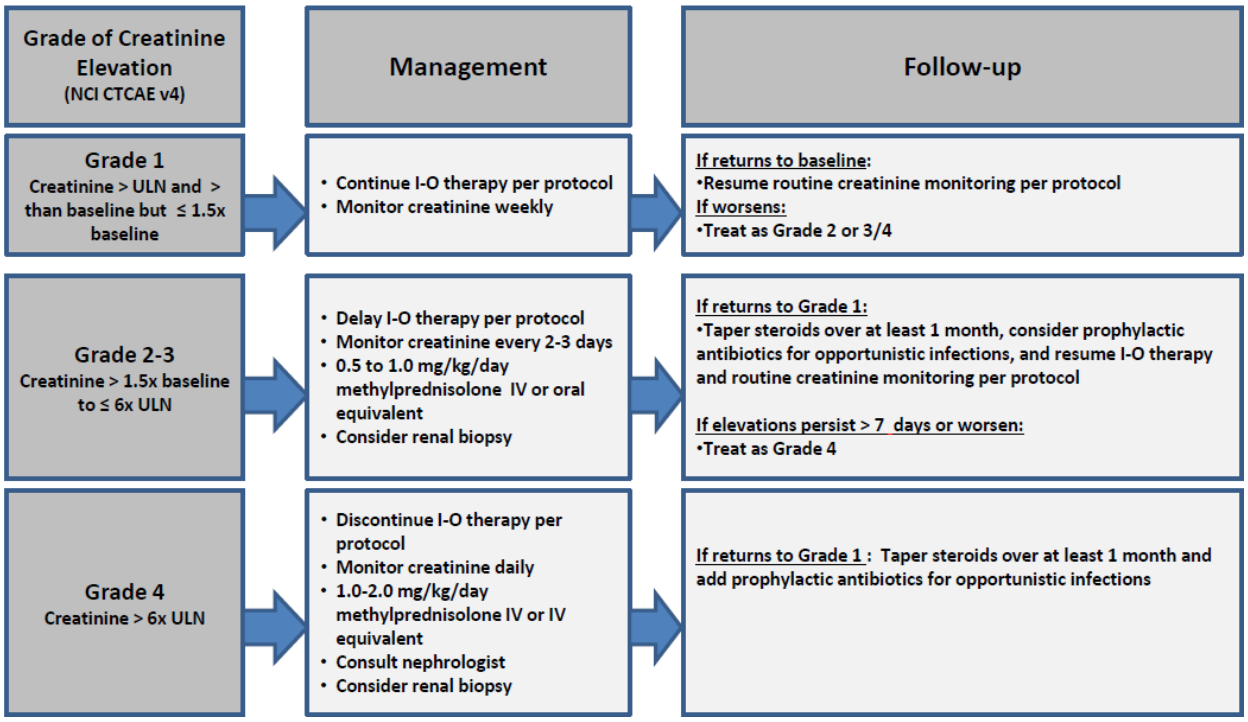
Colitis Management Algorithm



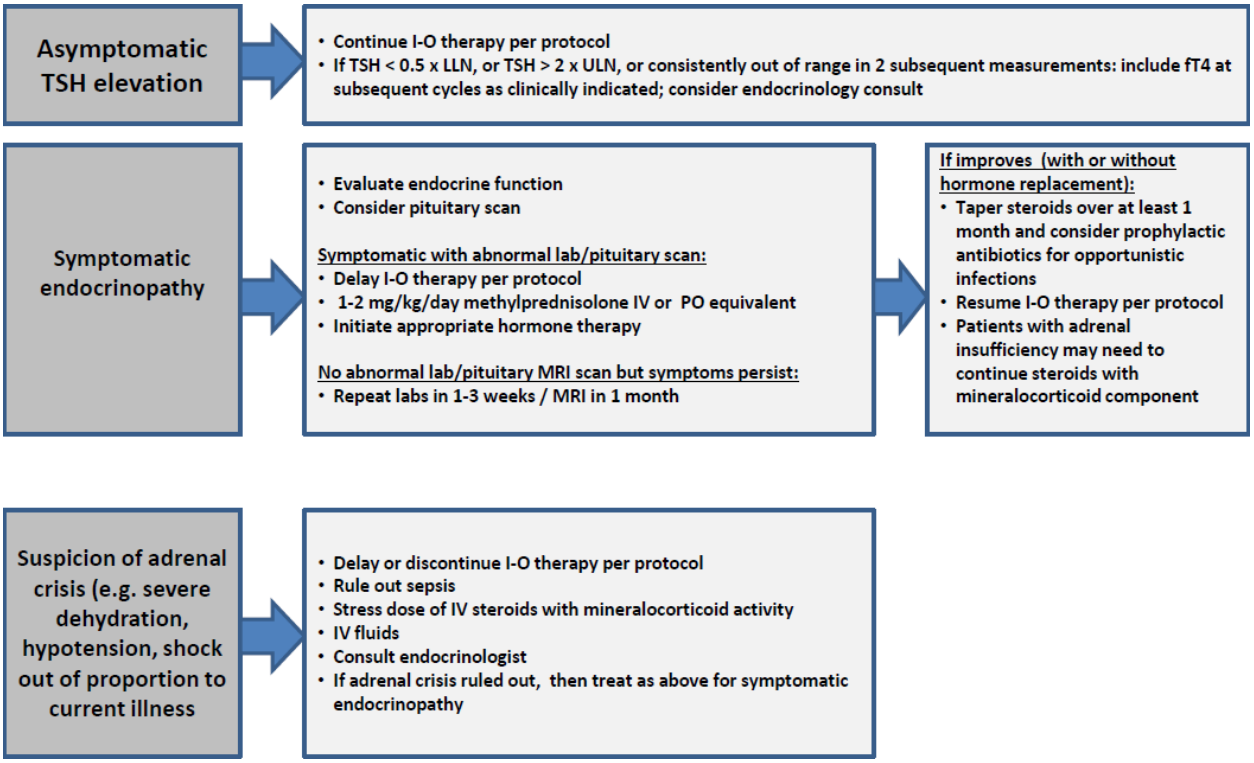
Hepatotoxicity Management Algorithm



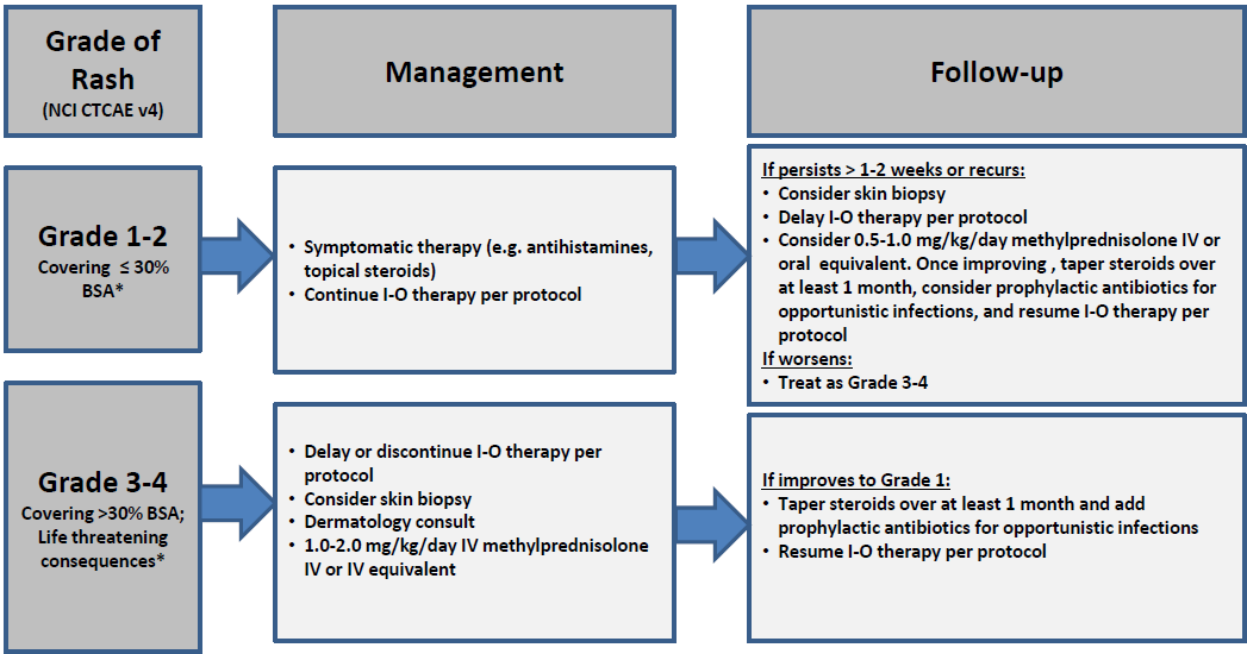
Renal Failure and Nephritis Management Algorithm



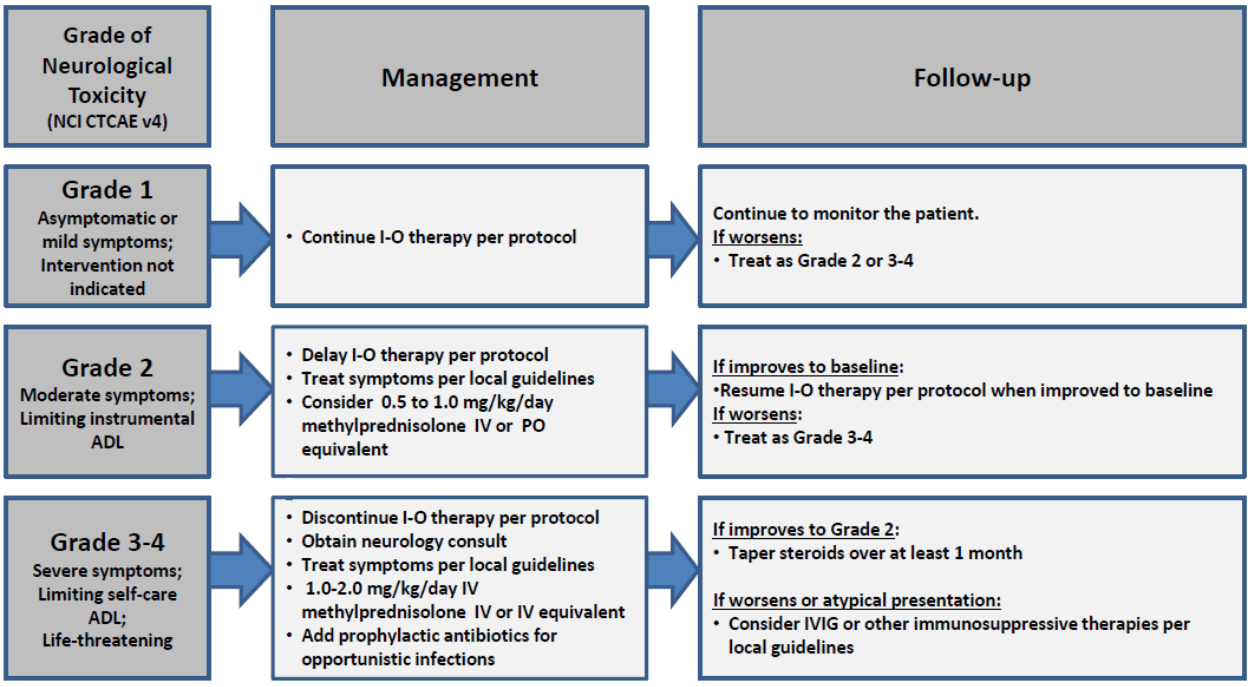
Endocrinopathy Management Algorithm



Skin Adverse Event Management Algorithm



Neurological Adverse Event Management Algorithm



9.5 Clinical Investigator Financial Disclosure

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 671		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 27		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 27 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)

1 See [web address].

- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

In accordance with 21 CFR 54.2, the Applicant submitted a list of the CA209037 study investigators attached to FDA form 3454 certifying that the Principal Investigators and Sub-investigators had no financial information to disclose as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the study. Fouad Namouni, MD, Vice President, Development Lead Nivolumab, certified this disclosure for the Applicant.

Financial disclosure information was collected and reported for 671, 668 Investigators (Principal Investigators and Sub-investigators) participating in Trial CA209037 and three independent radiology review committee readers from (b) (4) The Applicant states that all but three Investigators have signed Financial Disclosure Forms.

Out of the 668 Principal Investigators and Sub-investigators participating in Trial CA209037, 638 had no financial information to disclose. Disclosable interest information was provided for 27 Principal Investigators and Sub-investigators, all due to receipt of significant payments of other sorts. Financial disclosure information was not available for three Sub-investigators. The Applicant conducted due dilige0nce for the missing disclosures including three written requests and two telephone calls.

The three radiologist reviewers from (b) (4) who conducted the blinded, independent central review of tumor response and progression in Trial CA209037 did not report any disclosable information.

The following Investigators had disclosable financial information in the category of significant payments of other sorts:

- (b) (6) and Sub-investigators (b) (6) at sites (b) (6) receipt of funding from research grants during the conduct of the trial: $250,000 beginning (b) (6) $2,212,500 beginning (b) (6) beginning (b) (6) and $416,520 beginning (b) (6).
- (b) (6) Sub-investigator at site (b) (6) receipt of funding from research grants during the conduct of the trial: $136,450, $101,759, $65,000 and $85,000 all beginning (b) (6); $2,889,000 beginning (b) (6); $750,000 beginning (b) (6); and $30,000 and $170,502 both beginning (b) (6)
- (b) (6) Sub-investigator at site (b) (6) receipt of funding from research grants conducted during the

trial: $85,000 beginning [redacted]; and $150,000 beginning [redacted]

- [redacted] at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted]; $100,000 beginning [redacted]; and $3,344,500 beginning [redacted].
- [redacted] Investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $56,000 beginning [redacted] with a total of $156,250.
- [redacted] Sub-investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted]
- [redacted] Investigator at site [redacted] receipt of funding from research grants during the conduct of the trial: $100,000 beginning [redacted]; and $100,000 beginning [redacted]
- [redacted] Sub-investigator at site [redacted] In [redacted] he finalized a contract with BMS totaling $72,461 to support a [redacted] [redacted] reported that [redacted] with either clinical trial drug and does not pose any conflict of interest.
- [redacted] Investigator at site [redacted] $51,000 received for participating in the speaker's bureau during 2012-2013.
- [redacted] Investigator at site [redacted] $30,000 received for speaking honoraria
- [redacted] Investigator at site [redacted] $25, 000 received for participating in the speaker's bureau during 2012.

Three Investigators/ Sub-investigators did not provide Financial Disclosure as follows:

- [redacted] Sub-investigator at site [redacted] from [redacted]. The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site. [redacted] did sign [redacted] a Financial Disclosure Form for Study CA209067 that reported no disclosable interest.

- [redacted] Sub-investigator at site [redacted] from [redacted]. The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site.
- [redacted] Sub-investigator at site [redacted] from [redacted]. The Applicant states that they have contacted the site several times in writing and by phone to follow-up on obtaining a signed Financial Disclosure form and to request a forwarding address/contact details, as she had ended employment at the site. [redacted] did sign [redacted] a Financial Disclosure Forms for Study CA209025 and CA209067 that reported no disclosable interest.

A concern with respect to possible bias arose from the significant payments to the sites above. A subgroup analysis for efficacy was conducted whereby efficacy data from the 40 patients treated at sites 0016, 0020, 0023, 0028, 003, 0050, 0052, and 0067 were excluded. Excluding these sites did not impact the efficacy evaluation in the efficacy population.

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

/s/

MAITREYEE HAZARIKA
12/07/2014

MEREDITH K CHUK
12/07/2014

MARC R THEORET
12/07/2014

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: BLA125554 **Applicant: Bristol-Myers Squibb** **Stamp Date: 07/30/2014**

Drug Name: Nivolumab (OPDIVO) **NDA/BLA Type: BLA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			All documents are in English
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			As agreed to in the pre-BLA meeting
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			As agreed to in the pre-BLA meeting
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).			X	The Application is a BLA.
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?				
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)				
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: CA209003 Study Title: A Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 (MDX-1106) in subjects with selected advanced or recurrent malignancies			X	

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 395 Arms: 5 expansion cohorts Location in submission: BLA125554/SDN2/Module 5.3.5.3				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: CA209037 Indication: Subjects with advanced melanoma who have progressed on or after anti-CTLA-4 therapy and/or subjects with BRAF V600 mutations, who have progressed on or after a BRAF inhibitor in addition to anti-CTLA-4 therapy Pivotal Study #2: N/A Indication:	X			
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	There was no previous special protocol assessment agreement. However, FDA agreed that the endpoint of objective response rate in 120 patients followed for 6 months treated with nivolumab could be submitted for accelerated approval.
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	CA209037 is a multicenter international study, which included U.S, study sites conducted under IND115195.
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			Information is submitted from study CA209010 in metastatic RCC with 0.3, 2, and 10 mg/kg Q3W.
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	The patients are appropriate based on the serious and life-threatening indication.
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			The CA209037 safety datasets used MedDRA v 16.0.
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			BMS has requested a waiver for BLA125554 based on the orphan drug designation for nivolumab for the indication granted on January 23, 2013 for the treatment of Stage IIb to IV melanoma.
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	CA209037 is a multicenter international study, which included U.S,

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
					study sites conducted under IND115195.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _X_YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter

Maitreyee Hazarika, MD; Meredith Chuk, MD — September 22, 2014

Reviewing Medical Officer — Date

Maitreyee Hazarika, MD — September 22, 2014

Acting Team Leader — Date

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

/s/

MEREDITH K CHUK
09/22/2014

MAITREYEE HAZARIKA
09/22/2014