CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S) / STATISTICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Dickran Kazandjian, MD Sean Khozin, MD, MPH Lijun Zhang, PhD Shenghui Tang, PhD Gideon Blumenthal, MD (CDTL)
Review Completion Date	3/2/2015
Established Name	Nivolumab
(Proposed) Trade Name	Opdivo
Therapeutic Class	Monoclonal antibody
Applicant	Bristol-Myers Squibb
Formulation(s)	Intravenous
Dosing Regimen	3 mg/kg every two weeks
Indication(s)	Patients with squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy
Intended Population(s)	Second-line metastatic squamous NSCLC

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on review of the clinical data, the clinical and statistical team recommends traditional approval of OPDIVO (nivolumab) for the following indication:

> "*OPDIVO (nivolumab) is indicated for the treatment of patients with metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy*"

The basis of this recommendation is the favorable benefit-risk profile from study CA209017, an open-label, multicenter, multinational, randomized trial in patients with metastatic squamous NSCLC who had experienced disease progression during or after one prior platinum-based chemotherapy regimen. Patients received nivolumab (n=135), 3 mg/kg intravenously every 2 weeks, or docetaxel (n=137) 75 mg/m^2 intravenously every 3 weeks. The major efficacy outcome was OS. At a pre-specified interim analysis, nivolumab demonstrated a statistically significant improvement in OS as compared with docetaxel. Median OS was 9.2 months (95% CI: 7.3, 13.3) for patients assigned to nivolumab and 6 months (95% CI: 5.1, 7.3) for those assigned to docetaxel [Hazard Ratio 0.59; 95% CI: 0.44, 0.79, p=0.0003]. The OS curves appear to continue to separate beyond the medians.

These efficacy results were supported by the single arm, multinational, multicenter trial in patients with metastatic squamous (SQ) NSCLC who had progressed after receiving a platinum-based regimen and at least one additional systemic regimen, Study CA209063. Patients (n=117) received nivolumab, 3 mg/kg intravenously every 2 weeks. The major efficacy outcome measure was confirmed objective response rate (ORR) measured by a blinded independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). The ORR was 15% (95% CI: 9, 22). All were partial responses. At the time of analysis, the duration of response (DOR) was not reached, however, 10 of 17 (59%) of responding patients had responses of 6 months or longer.

The most common adverse reactions among the 117 patients receiving nivolumab in the single arm CA209063 trial in patients with metastatic SQ NSCLC were ($\geq$ 30% fatigue, dyspnea, musculoskeletal pain, decreased appetite, and cough. The most frequent Grade 3 and 4 adverse drug reactions observed in at least 5% of patients treated with nivolumab were dyspnea, fatigue, and pneumonia. The most common worsening laboratory abnormalities ($\geq$10% Grades 3-4) were lymphopenia and

hyponatremia. Immune-mediated adverse events were generally consistent with what was observed with melanoma and included: pneumonitis (6%), colitis (0.9%), nephritis/renal dysfunction (0.9%), hypothyroidism (4%), and hyperthyroidism (1.7%). The majority of immune-mediated adverse events could be effectively managed with corticosteroids and/or dose interruption.

In April 2014, FDA (b) (4) requested top-line OS data from the 017 randomized study. On December 19, 2014, FDA received a password-protected report from Dr Mathias Hukkelhoven of BMS. The report was from the independent statistical contractor that supported the external Data Monitoring Committee (DMC). Per the sponsor, this report remained blinded to all others in BMS. Based on these results, FDA contacted Dr Hukkelhoven to notify him that the NSCLC BLA should be submitted. On January 10, 2015, the independent DMC met and recommended that the 017 study be declared positive and patients randomized to the docetaxel control arm be allowed to cross-over to receive nivolumab.

Based on the top-line results of the 017 study, in which a statistically significant and clinically meaningful improvement with nivolumab against the active control docetaxel was demonstrated, the clinical and statistical team committed to an expeditious review of this BLA for a patient population with high unmet medical need lacking effective available therapies.

1.2 Risk Benefit Assessment

Lung cancer is the leading cause of cancer-related death in the U.S. and worldwide. Approximately 87% of all lung cancer are classified as non-small cell lung cancer (NSCLC). When feasible, surgical resection is the treatment of choice for localized disease. However, the majority of patients diagnosed with lung cancer have advanced or metastatic disease. Patients with advanced NSCLC who receive no treatment survive a median of 4 months after diagnosis.

Metastatic SQ NSCLC has high unmet medical need. In newly diagnosed patients, the standard of care is platinum-doublet based chemotherapy, which leads to median survival of approximately 8 to 12 months. In patients who progress after platinum-doublet chemotherapy, available therapies include docetaxel (with a response rate of 5 to 12% and median survival of 6 to 9 months), docetaxel with ramucirumab (with response rates of approximately 25% and median survival of 10 months), and erlotinib (with response rate of 5 to 9% and median survival of 7 months). In contrast to EGFR mutation or ALK rearrangement in patients with adenocarcinoma, there has been little progress in the development of highly effective treatments for the treatment of SQ

NSCLC. Therefore, new therapies are needed to cure, improve OS, substantially delay disease progression, or ameliorate symptoms for metastatic SQ NSCLC.

In Study CA209017, nivolumab met its pre-specified interim OS endpoint. A statistically significant and clinically meaningful improvement in survival was observed, with a median OS improvement of 3.2 months compared to docetaxel, (9.2 months for patients randomized to the nivolumab arm and 6.0 months for patients randomized to the control arm). This benefit was associated with a relative risk decrease of 41% (HR: 0.59; 95% CI: 0.44, 0.79; p=0.00025). The OS curves appeared to continue to separate after the medians, which may reflect enhanced efficacy at the tail of the curve.

Efficacy was supported by the single arm CA209063 trial which demonstrated an ORR of 14.5% (95% CI: 8.7, 22.2) for nivolumab in heavily pre-treated patients. These responses were durable with the median duration of response not being reached and of the 17 patients with confirmed responses, 13 (76%) having ongoing responses ranging from 1.9+ to 11.5+ months. Of these 17 patients, 10 (59%) had durable responses of 6 months or longer.

The most common (greater than or equal to 30%) adverse reactions and laboratory abnormalities among the 117 patients receiving nivolumab in the single arm CA209063 trial in patients with metastatic SQ NSCLC included fatigue, lymphopenia, dyspnea, decreased appetite, and cough. The most frequent Grade 3 and 4 adverse drug reactions and laboratory abnormalities observed in at least 5% of patients treated with nivolumab included dyspnea, fatigue, lymphopenia, and hyponatremia. Clinically significant immune-mediated adverse reactions included pneumonitis (6%; five were Grade 3 and two were Grade 2), colitis (one case of Grade 3), nephritis/renal dysfunction (one case of Grade 2), hypothyroidism (4.3%; all cases treated with levothyroxine and no patients required interruption in nivolumab dosing), and hyperthyroidism (1.7%). These immune-mediated adverse reactions were generally managed by supportive measures including corticosteroids and/or interruption of nivolumab dosing. The incidence of immune-mediated pneumonitis in particular appears to be higher in NSCLC than in melanoma and therefore FDA requested further characterization of immune-mediated adverse events in the randomized study as a post-marketing requirement.

In summary, given the relative lack of efficacious treatments for SQ NSCLC, nivolumab presents patients with a significant improvement in treatment options as observed by a clinically meaningful improvement in OS compared to the active control docetaxel and therefore the FDA clinical team recommends the granting of regular approval of nivolumab for the second-line treatment of patients with squamous NSCLC.

Table 1: Benefit-Risk Analysis for nivolumab in the treatment of patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy (Source: FDA; Reviewer Table)

Disease	Patients with metastatic squamous NSCLC who have progressed on or after front-line platinum-based doublet chemotherapy have a serious and life-threatening condition with historic median survival rates of 8-10 months with minimal available therapies.
Unmet medical need	Metastatic squamous NSCLC patients who progressed after front-line therapy have few options and are usually treated with standard cytotoxic chemotherapy. The currently available therapies include docetaxel with or without ramucirumab and erlotinib which are associated with low response rates (ORR: 5 to 22%) with substantial toxicity.
Clinical benefit	In a randomized trial comparing nivolumab to standard of care docetaxel, nivolumab was associated with a 3 month increase in median survival and a 41% risk reduction in death. The survival curves appeared to continue to separate after the medians. In a second single arm study, nivolumab was associated with a 15% IRC ORR with 59% of responders maintaining their responses at 6 months. All responders continued to be alive at the time of the database lock.
Risk	The most common adverse reactions and laboratory abnormalities in patients receiving nivolumab included fatigue, lymphopenia, dyspnea, decreased appetite, and cough. The most frequent Grade 3 and 4 adverse drug reactions and laboratory abnormalities observed in patients treated with nivolumab included dyspnea, fatigue, lymphopenia, and hyponatremia. Clinically significant immune-mediated adverse reactions included pneumonitis, colitis, nephritis/renal dysfunction, hypothyroidism, and hyperthyroidism. These immune-mediated adverse reactions were managed with supportive measures including corticosteroids and/or interruption of nivolumab dosing suggesting that immune-related toxicities can be reasonably managed with dose interruptions and supportive care.
Uncertainties	The randomized trial demonstrating an improvement in overall survival confirmed the clinical benefit observed with ORR in the single arm trial. However, further studies will be needed to identify better predictive biomarkers and to explore the utility of PD-L1 testing to predict clinical benefit. Additional data is also needed to assess the long-term outcomes of the immune-related adverse events and their management.
Conclusions	Nivolumab meets the criteria for traditional approval based on a favorable benefit-risk profile for the treatment of patients with metastatic squamous NSCLC who have progressed on or after treatment with a first-line platinum-based doublet regimen. Nivolumab demonstrated an improvement over currently available therapies with a risk profile acceptable compared to the clinical benefit offered.

Abbreviations: NSCLC, non-small cell lung cancer; ORR, objective response rate; IRC, independent review committee; CNS, central nervous system; DOR, duration of response;

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No REMS or Medication Guide is required for marketing of nivolumab.

1.4 Recommendations for Postmarket Requirements and Commitments

The clinical team recommends the following Postmarketing Requirement (PMR):

Conduct a randomized trial that will characterize the incidence, severity and response to treatment of nivolumab induced immune-mediated adverse reactions to include immune-mediated pneumonitis.

Rationale: In the single arm SQ NSCLC study, a relatively high rate of immune-mediated pneumonitis (6%) was observed. Patients with NSCLC may be at higher risk for immune-mediated pneumonitis as compared to patients with melanoma given the anatomic region of the malignancy, other co-morbidities, and prior radiotherapy to the thorax. Updated safety data from the randomized 017 study in second-line SQ NSCLC is necessary to better characterize immune-mediated pneumonitis in this patient population.

The clinical team recommends the following Postmarketing Commitment (PMC):

Submit the Clinical Study Report and efficacy datasets for the open-label randomized trial of nivolumab versus docetaxel in patients with previously treated advanced squamous non-small cell lung cancer.

Rationale: In the randomized, open-label, multicenter, multinational study of OPDIVO versus docetaxel in patients with metastatic SQ NSCLC, the data monitoring committee terminated the study at a planned interim analysis due to an OS benefit observed with patients allocated to OPDIVO. As a PMC, the CSR and efficacy datasets are needed to further characterize OS, progression-free survival, and overall response rate.

2 Introduction and Regulatory Background

Lung cancer is the second most common cancer after prostate cancer in men and breast cancer in women. Estimates for lung cancer in the United States for 2014 (American Cancer Society) are 224,210 new cases, with 159,260 deaths, and accounts for 27% of all cancer deaths. It is the leading cause of cancer death with more people dying of lung cancer than of colon, breast, and prostate cancers combined. The average age at the time of diagnosis is about 70.[1] Lung cancer incidence has been declining among men over the past 20 years and is now declining among women. Survival in lung cancer depends on the stage of disease at diagnosis.

Lung Cancer is broadly divided into two categories, non-small cell lung cancer (~85%) and small cell lung cancer. Non-small cell consists of two major histologic subtypes: adenocarcinoma and squamous cell carcinoma. The mainstay for curative treatment involves surgery and adjuvant platinum-based doublet chemotherapy, depending on the

stage of disease. Five year survival for treated Stage I cancers are 50% and decline with advanced stages (Stage II: 30%; Stage III: 10%; Stage IV: 1%).[1] Overall, 5 year survival is a dismal 16%. There are a number of risk factors in the development of lung cancer thus far identified but the leading one is exposure to cigarette smoke.[2]

Cytotoxic chemotherapy is the backbone of treatment for patients with advanced NSCLC. Standard platinum doublets are the mainstay and result in median survivals of approximately 8 to 10 months. With the advent of targeted therapeutic approaches, a number of novel agents such as monoclonal antibodies, antibody directed conjugates and small molecule kinase inhibitors have been developed to target specific molecular aberrations. [3] One of the most studied "driver" pathways has been the EGFR and k-RAS pathways. EGFR tyrosine kinase inhibitors such as erlotinib, gefitinib and afatinib have been found to benefit mostly patients with drug sensitive EGFR mutations (present in about 20% of patients with adeno NSCLC). There are a number of other genetic "driver mutations" which have recently been discovered. Crizotinib and ceritinib are FDA approved for patients with NSCLC whose tumors harbor ALK rearrangements (present in about 5% of adeno NSCLC).[4] Figure 1 below describes the most recent identified genetic lesions and possible drug targets for development.

Figure 1: Proportion of Specific Molecular Alterations in Adeno and Squamous Lung Carcinoma[5]

Although there have a number of recent advances and drug approvals in lung adenocarcinoma, novel treatments for SQ NSCLC are lacking. Given the different biology of SQ NSCLC, patients with this histology have not benefited from novel treatments despite encompassing 30% of all NSCLC cases.

A relatively newer therapeutic drug modality is immune based blockade therapy. Specifically, pathways involved in inhibiting anti-tumor T cell responses allow tumors to evade the immune system. T cells, in order to become activated, require engagement of their T cell receptor and a stimulation of a co-receptor. The figure below shows the various activating and inhibiting co-receptors. Activation of the inhibitory co-receptors CTLA-4 and programmed cell death 1 (PD-1) on T cells with their ligands, B7 and PD-L1/2 are found on antigen presenting cells and in the case of PDL1/2 also on tumor cells.

Figure 2: T Cell Costimulatory pathways[6]

The figure below demonstrates the interaction of a tumor cell with an effector T Cell and subsequent inhibition of anti-tumor T cell responses.

Figure 3: PD-1 Engagement and Evasion[7,8]

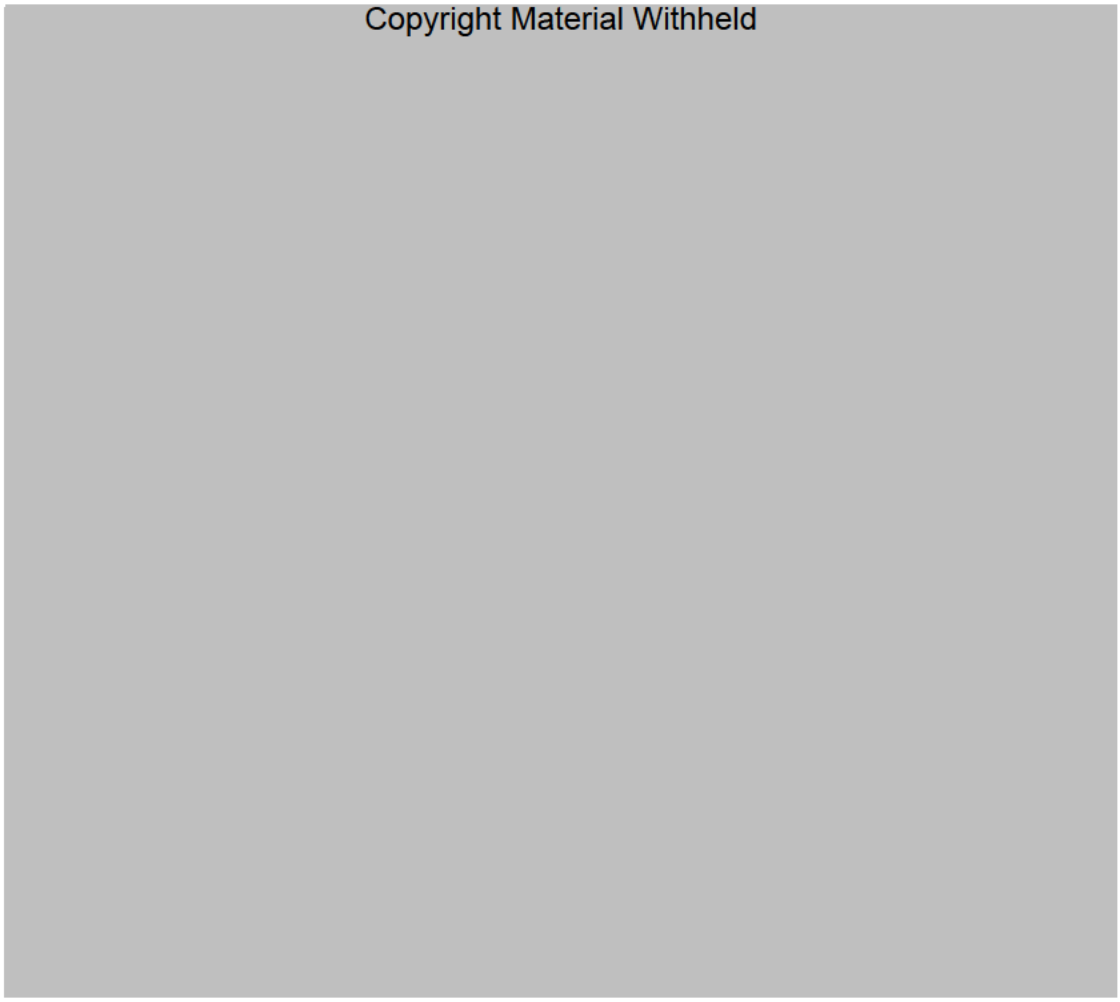


Figure 4: PD-1 engagement with PD-L1 on APCs and Tumors[8]

Given these co-stimulatory inhibitory pathways, drugs which target these interactions may provide a therapeutic opportunity in cancer. Currently, ipilimumab an anti-CTLA4 monoclonal antibody and nivolumab and pembrolizumab anti-PD1 monoclonal antibodies are approved for the treatment of advanced melanoma. The figure below depicts how engagement of a monoclonal antibody to PD1 might prevent the down regulation of T cells. Recently, a number of PD1/PDL1 inhibitors have been tested in NSCLC, and early phase trials have suggested activity. The biggest risk factor for SQ NSCLC is exposure to tobacco and the resultant tumor promoting DNA damage that is caused. Preliminary evidence suggests that two types of cancers (melanoma and NSCLC) associated with the highest level of somatic mutations respond to immune-based therapies including PD-1 immune check point blockers.[9] In addition, antibodies blocking the PD-1 axis might have more activity in smokers. It is hypothesized that carcinogens including tobacco induce vast mutational heterogeneity which leads to expression of inhibitory co-receptors such as PD-L1 on the tumor. Furthermore, previous DNA damage causing treatment for these cancers might induce upregulation of PD-L1.

Figure 5: Antibody Blockage of PD-1 Signal[8]

2.1 Product Information

Nivolumab, also referred to as BMS-936558, MDX-1106, or ONO-4538, is marketed in the US by Bristol-Myers Squibb (BMS) under the trade name OPDIVO. Nivolumab first received Accelerated Approval for unresectable or metastatic melanoma in the U.S. in December 2014 based on single arm studies demonstrating beneficial tumor response rate and durability of response. The recommended dose of OPDIVO is 3 mg/kg administered as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity. There are no dose reduction recommendations. The dosage forms include 40 mg/4 mL and 10 mg/mL solution in a single-use vial.

Nivolumab is a human monoclonal antibody of the IgG4 class consisting of (b) (4) Its molecular weight is 146,221 Daltons and its molecular formula is $C_{6462}H_{9990}N_{1714}O_{2074}S_{42}$.

Figure 6: cDNA-Derived Amino Acid Sequences of Heavy and Light Chains of Nivolumab (Applicant Figure; Source: 3.2.S Drug Substance)

Nivolumab's appearance is clear to opalescent, colorless to pale yellow liquid, and its solution pH is (b) (4) The extinction coefficient for nivolumab is calculated to be (b) (4). The isoelectric point of the predominant form is approximately (b) (4)

Nivolumab, a human monoclonal immunoglobulin G4 (IgG4) antibody, is a specific programmed death-1 (PD-1) immune checkpoint inhibitor. PD-1 has important T-cell regulatory functions, but does not mediate antibody-dependent cell-mediated cytotoxicity (ADCC) of activated human T cells.

2.2 Tables of Currently Available Treatments for Proposed Indications

Nivolumab is a targeted therapy currently approved and being used clinically for metastatic melanoma. While there are currently two approved anti-PD1 drugs for melanoma, none are approved for NSCLC. FDA approved regimens for NSCLC in the first-line setting and subsequent settings are described in Table 1 and 2.

Table 2: Currently available FDA-approved chemotherapeutic agents for first-line treatment of advanced SQ NSCLC (Source: FDA; Reviewer Table)

Drug	1st Line Treatment	Efficacy

Docetaxel	Unresectable, locally advanced or metastatic NSCLC in combination with cisplatin	Docetaxel + cisplatin vs vinorelbine + cisplatin with primary endpoint OS:
		mOS: 10.9 vs 10.0 months; OS HR: 0.88 (0.74-1.06) p=0.122;
		mTTP: 21.4 (19.3-24.6) vs 22.1 (18.1-25.6) weeks; p=NS;
		ORR: 31.6% (26.5-36.8) vs 24.4% (19.8-29.2) p=NS

Gemcitabine	Inoperable, locally advanced (Stage IIIA or IIIB), or metastatic (Stage IV) NSCLC in combination with cisplatin	1. Gemcitabine + cisplatin vs cisplatin with primary endpoint OS:
		mOS: 9.0 (8.2-11.0) vs 7.6 (6.6-8.8) months p=0.008;
		mTTP: 5.2 (4.2-5.7) vs 3.7 (3.0-4.3) months p=0.009
		ORR: 26% vs 10%
		2. Gemcitabine + cisplatin vs etoposide + cisplatin with primary endpoint OS:
		mOS: 8.7 vs 7.0 months p=0.18
		mTTP: 5.0 vs 4.1 months p=0.015;
		ORR: 33% vs 14% p=0.01

Nab-paclitaxel	Locally advanced or metastatic NSCLC, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy	Nab-paclitaxel + carboplatin vs paclitaxel + carboplatin with primary endpoint IRC ORR: IRC ORR: 33% (28.6-36.7) vs 25% (21.2-28.5) p=0.005; mDoR: 6.9 (5.6-8.0) vs 6.0 (5.6-7.1) months
Paclitaxel	In NSCLC patients in combination with cisplatin who are not candidates for curative surgery and/or radiation	Paclitaxel + cisplatin vs etoposide: mOS: 9.3 vs 7.4 months p=0.08; mTTP: 4.3 vs 4.9 months p=0.004 ORR: 25% vs 12% p<0.001
Vinorelbine	Unresectable, advanced NSCLC as a single agent or in combination with cisplatin for treatment of ambulatory patients	1. Vinorelbine + cisplatin vs cisplatin with primary endpoint OS: mOS: 7.8 (6.9-9.6) vs 6.2 (5.4-7.7) months p=0.01; ORR: 19% vs 8% 2. Vinorelbine + cisplatin vs vindesine + cisplatin with primary endpoint OS: mOS: 9.2 (7.4-11.1) vs 7.4 (6.1-9.1) months p=0.087 ORR: 28% (22-35) vs 19% (14-25) p=0.03

Table 3: Currently available FDA-approved second line chemotherapeutic agents for advanced NSCLC (Source: FDA; Reviewer Table)

Drug	NSCLC Refractory Indication	Efficacy
Docetaxel	Locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy	1. Docetaxel vs ifosfamide or vinorelbine with primary endpoint OS: mOS: 5.7 (5.1-7.1) vs 5.6 (4.4-7.9) months; OS HR: 0.82 (0.63-1.06) p=0.13; mTTP: 8.3 (7.0-11.7) vs 7.6 (6.7-10.1) weeks ; ORR: 5.7% (2.3-11.3) vs 0.8% (0.0-4.5) 2. Docetaxel vs best supportive care with primary endpoint OS: mOS: 7.5 (5.5-12.8) vs 4.6 (3.7-6.1) months; OS HR: 0.56 (0.35-0.88); p=0.01 mTTP: 12.3 (9.0-18.3) vs 7.0 (6.0-9.3) weeks ; ORR: 5.5% (1.1-15.1) vs n/a
Erlotinib	Locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen	Erlotinib vs Placebo with primary endpoint OS : mOS: 6.7 vs 4.7 months; OS HR: 0.73 (0.61-0.86) p<0.001; mPFS: 9.9 vs 7.9 weeks; PFS HR: 0.59 (0.50-0.70) p<0.001; ORR: 8.9% vs 0.9% p<0.001
Ramucirumab + Docetaxel	In combination with docetaxel for metastatic NSCLC with disease progression on or after platinum-based chemotherapy.	Docetaxel + Ramucirumab vs Docetaxel + placebo with primary endpoint OS: mOS: 10.5 (9.5-11.2) vs 9.1(8.4-10.0) months; OS HR: 0.86 (0.75-0.98) p=0.024; mPFS: 4.5 (4.2-5.4) vs 3.0 (2.8-3.9) months; PFS HR: 0.76 (0.68-0.86) p<0.001; ORR: 23% (20-26) vs 14% (11-17) p<0.001

Reviewer Note: Regimens approved for squamous NSCLC include erlotinib or docetaxel with or without ramucirumab.

2.3 Availability of Proposed Active Ingredient in the United States

OPDIVO® is currently marketed in the United States for the following approved indication:

For the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and if BRAF V600 mutation positive, a BRAF inhibitor.

2.4 Important Safety Issues With Consideration to Related Drugs

The important safety issues of marketed OPDIVO include:

1. Immune-mediated pneumonitis
2. Immune-mediated colitis
3. Immune-mediated hepatitis
4. Immune-mediated nephritis and renal dysfunction
5. Immune-mediated hypothyroidism and hyperthyroidism
6. Other immune-mediated adverse reactions

In addition, KEYTRUDA contains a warning on Immune-Mediated Hypophysitis. YERVOY has a black box warning for immune-mediated adverse reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

- The initial IND was submitted on June, 28 2006 and was found to be safe to proceed. In July 2008, a Phase 1b dose finding protocol was submitted to the IND.

- An EOP1/pre-Phase 3 meeting with FDA Division of Oncology Products 2 (DOP2) to discuss the Phase 3 NSCLC program occurred in December 2011. The purpose of the meeting was review preliminary data from the Phase 1 study CA209003 and to receive FDA feedback and agreement on the clinical pharmacology plan for development and registrational plan in NSCLC and specifically, the efficacy trial, CA209017.

    - The proposed methodology and rationale to support selection of the dose and regimen for phase 3 development was reasonable.
    - In general, the proposed clinical pharmacology plans including PK characterization, immunogenicity, and QT evaluation was acceptable but FDA asked to include race as a covariate in the proposed population PK analysis.
    - FDA generally agreed with the overall design of CA209017.
    - FDA agreed with the proposed methods of analysis for the primary and secondary endpoints and gave feedback on landmark analyses.
    - FDA asked BMS to include Serious Adverse Event (SAE) that were not treatment related, and a few other laboratory variables.

  - FDA gave feedback on the applicability of a single randomized study.

- In May 2012, a Type A meeting with DOP2 occurred to discuss the squamous and non-squamous NSCLC development strategy and potential for accelerated approval regulatory pathway for squamous NSCLC.

  - FDA agreed to the splitting based on histology for the NSCLC program.
  - Regarding accelerated approval, FDA stated that whether demonstration of a statistically significant effect on objective response rate, in the absence of a detrimental effect on survival in an interim analysis would be sufficient to support a request for accelerated approval will depend on the magnitude of the treatment effect and the risk:benefit evaluation.
  - FDA recommended that overall survival (OS) for the randomized study should be the primary endpoint and that single arm objective response rate (ORR) data may be supportive.

- June 2012, Fast Track Designation was granted for demonstration of improved OS, progression free survival (PFS) and ORR compared to standard second line treatment (docetaxel monotherapy) for the treatment of patients with metastatic SQ NSCLC with disease progression during or after their first systemic therapy (b) (4) .

- July 2012, protocols CA209017 and CA209057 were submitted to the IND and on October 2012, CA209063 was submitted.

- (b) (4) .

- February 2014, Fast Track Designation was amended to include the indication of NSCLC which has progressed following cisplatin-doublet chemotherapy and at least 1 additional systemic therapy.

- April 2014, a pre-BLA meeting for refractory SQ NSCLC was held and a rolling review was granted. Part 1 (nonclinical) of the BLA was submitted.

  - FDA stated that based on the data provided, FDA believes that submission of an application based on the results from (b) (4) is premature. (b) (4) . The magnitude of an effect on durable ORR in support of accelerated approval should have a sufficiently high magnitude of effect in order to predict clinical benefit.

Therefore, FDA does not agree that data from studies (b) (4) could form the basis for submission of a BLA for potential accelerated approval of nivolumab in the treatment of refractory squamous NSCLC patients. If BMS elects to submit a BLA based only on this data, the application would be referred to an ODAC.

- FDA strongly recommended that BMS delay submission of the proposed BLA until the planned interim analysis for the ongoing CA209017 trial is conducted. It would be acceptable to initiate a rolling BLA in which the CMC, Nonclinical, and Clinical Pharmacology modules are submitted; however, the clinical module should not be provided until the completion of the planned interim analysis of study CA209017. If the data from study CA209017 demonstrates a statistically significant robust effect on OS, FDA would work closely with BMS to expedite the submission and review of the clinical module.
- FDA gave feedback on the proposed presentation of the Adverse Reactions section of the nivolumab draft USPI. (b) (4) should not be included. FDA stated that in single arm studies, in general, it is very difficult to determine accurate drug causality given the imprecision in investigator-based causality attribution.
- FDA agreed with the proposal regarding the Summary Level Clinical Site Data for study CA209063.
- At the time of BLA submission, FDA recommended submission of a specific financial disclosure information format.

- June 2014, Part 2 of the BLA was submitted which included CMC and Clinical Pharmacology

- July 2014, BLA 125554 was submitted for advanced melanoma

- December 19, 2014, FDA received the blinded DMC report of the interim OS results from Study CA209017. Based on the results of this DMC report and the fairly mature interim OS analysis results, FDA informed the sole un-blinded BMS contact to submit the final clinical module to complete the BLA submission for the SQ NSCLC indication. The final clinical module included the clinical efficacy and safety results from Study CA209063. In addition, BMS agreed to submit the legacy data sets used by the DMC to analyze the efficacy results from Study CA209017.

- December 22, 2014, nivolumab received accelerated approval for the indication of the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and if BRAF V600 mutation positive, a BRAF inhibitor.

2.6 Other Relevant Background Information

3 Ethics and Good Clinical Practices

Trial CA209063 (A Single-Arm Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens) appears to have been conducted in adherence to Good Clinical Practices. There were no significant concerns with the Applicant's submission facilitating a review consistent with Good Review Management Principles and Practices for PDUFA Products.

3.1 Submission Quality and Integrity

The submission by BMS contains all the components of e-CTD. In general, it was well organized and allowed for substantive review of the contents. Specifically, regarding the pivotal Study CA209063, 27 medical sites enrolled patients in 4 countries.

Figure 7: Graphic representation of number of patients enrolled per site and country for study CA209063 (Source: CA209063 dataset; Reviewer Figure)

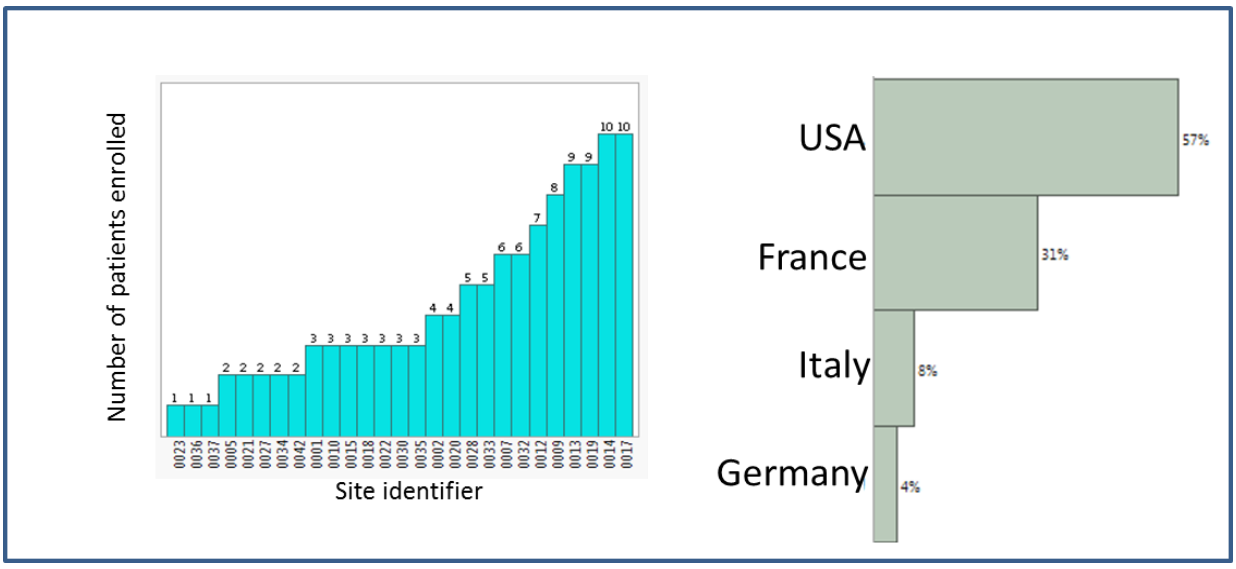
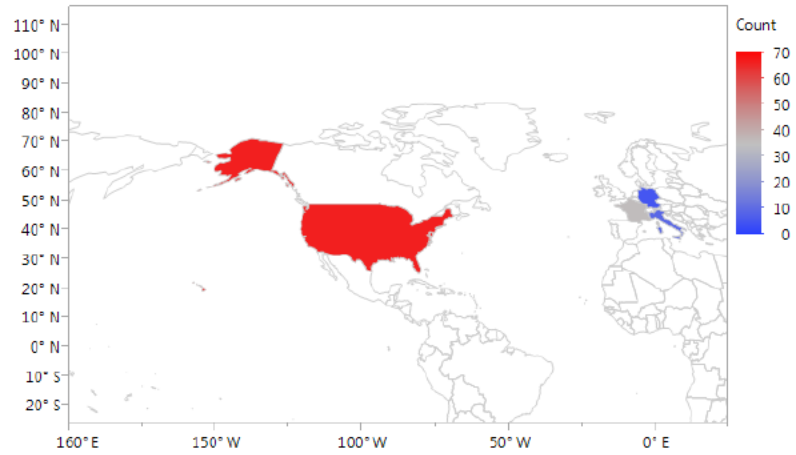


Figure 8: Country Colored by Patient Frequency (Source: CA209063 dataset; Reviewer Figure)



To evaluate for any potential differences in clinical sites and countries, FDA conducted subgroup analysis of the primary endpoint, independent review committee (IRC) assessed ORR to verify no significant outlying center or nation.

Table 4: Number of patients and respective ORR for each enrolling country (Source: CA209063; Reviewer Table)

Country	Number of Patients Enrolled	Country specific ORR (95%CI)
Entire Study	**n=117**	**14.5% (2.9, 11.8)**
USA	67	17.9%
France	36	11.1%
Italy	9	11.1%
Germany	5	0

Given the number of study centers, FDA analyzed ORR of the study with the top three enrolling centers each individually removed to evaluate if any particular high enrolling sites biased the results.

Table 5: Highest enrolling sites, ORR of individual sites, and ORR if site is excluded (Source: CA209063; Reviewer Table)

Site Number	Country	Number of Patients Enrolled	Site specific ORR	Study ORR excluding site ORR (95%CI)
Entire Study		**117**	**14.5% (2.9, 11.8)**	
0017	USA	10	10.0%	15.0% (9.4, 22.9)
0014	France	10	0	15.9% (10.2, 24.0)
0013	USA	9	33.3%	13.0% (7.9, 20.6)
0019	France	9	33.3%	13.0% (7.9, 20.6)
009	USA	8	12.5%	14.7% (9.2, 22.5)

Upon analysis, no site significantly contributed to the overall ORR. Furthermore, sensitivity analyses looking for questionable records in the data sets were performed. For example, no subjects had duplicates for date of birth. Laboratory values were looked at to determine duplicate constant laboratory findings. Site 00.19 had the most duplicate findings however, they were distributed between a number of patients. Patient 63095 from site 0002 had the most individual duplicate results. Therefore, no investigations were initiated by Office of Scientific Investigation for study 063.

For the Nivolumab BLA submission for melanoma, DOP2 consulted the Office of Scientific Investigation (OSI) to perform an audit of three clinical study sites and the Contract Research Organization (CRO) (b) (4) to identify any data quality issues and to document that the study was performed according to GCP. No significant issues were identified during these inspections, except for one site where a Form FDA 483 was to the site issued for minor deviations.

In addition, FDA's Jump Start Service was consulted to evaluate data fitness. The data sets, except for some minor issues, conformed to FDA's CDISC standards.

3.2 Compliance with Good Clinical Practices

The sponsor stated that the laws and regulatory requirements of all countries that had sites participating in this study were adhered to. The sponsor stated that the study was conducted in accordance with Good Clinical Practice (GCP), 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). No breaches of the conditions and principles of GCP in connection with the study or protocol were reported.

3.3 Financial Disclosures

The Sponsor included the list of investigators organized by country and site along with CVs of the investigators and Sponsors for study CA209063 and CA20937 as separate documents found in module 1.3.4 of the eCTD. In addition, the CSR also contains similar information. Regarding the covered trials (CA209063 and CA20937), BMS disclosed financial arrangements with investigators as recommended in the FDA guidance on Financial Disclosure by Clinical Investigators. Financial disclosure information was collected and reported for 298 Investigators (Principal Investigators and Subinvestigators) participating in CA209063. All but one Investigator signed the Financial Disclosure Forms. The one investigator who did not sign a BMS Financial Disclosure Form was a subinvestigator who for medical personal reasons was removed from the investigator list (Dr. (b) (6)).

Forms were reviewed by BMS, or designee. In cases where designee (CRO) is managing the trial, the CRO is responsible for review and communication of any issues with a disclosure form to the site and/or BMS. Disclosable information included:

- Investigators who indicated disclosable interest on the form were requested to provide additional information to specify the details of the disclosable interest.
- The Financial Disclosure form and additional information provided detailing the financial interest were reviewed to determine site participation in the trial and the potential bias presented by the disclosable interest.
- The decision on site participation for an Investigator with a disclosable interest is documented in a memo including the following information: objective of trial, size of site enrollment contribution relative to overall study size, and use of an independent committee

BMS' due diligence process includes three written requests (sent by traceable mail) and two documented telephone calls. No disclosable information was reported for the independent radiology reviewers. Dr. (b) (6) (Principal Investigator) and Dr.s (b) (6) (sub investigators) at site (b) (6) which enrolle (b) (6) patients reported the following: Significant payments of other sorts due to their participation in the (b) (6) for funding from research grants were reported. These included $100,000 over a year starting from November 2012, $100,000 over a year starting from March 2013, and $3,344,500 over 4 years starting from April 2013. BMS concluded that potential bias is limited given that an IRC was used to evaluate the primary endpoint.

Reviewer Note: While significant contributions were made to Dr (b) (6) and colleagues, the reviewer agrees that since an IRC was used and that only (b) (6) patients were enrolled from this site, it is highly unlikely that any bias affected the final results of this study.

Dr. (b) (6), a subinvestigator from site (b) (6) reported disclosable financial information in the category of significant payments of other sorts. Specifically, he received a $200,000 one-year educational grant from BMS for December 2011 (b) (6) . His salary from the project was approximately $11,000.

Reviewer Note: The reviewer agrees that since an IRC was used, it is highly unlikely that any bias affected the final results of this study. In addition, the grant was awarded for a project not directly related to nivolumab.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

There was no new CMC information or data submitted for this sBLA. Please see the recent melanoma approval for this information.

4.2 Clinical Microbiology

There was no new microbiology information or data submitted for this sBLA. Please see the recent melanoma approval for this information.

4.3 Preclinical Pharmacology/Toxicology

There was no new preclinical information or data submitted for this sBLA. Please see the recent melanoma approval for this information.

4.4 Clinical Pharmacology

For full details, please see Clinical Pharmacology review by Dr Xianhua (Walt) Cao and Dr. Hongshan Li.

4.4.1 Mechanism of Action

As reported by the sponsor, in vitro, nivolumab binds to PD-1 with an EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ~ 1 nM). However, it does not bind to related members of the CD28 family such as CD28, ICOS,

CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in enhancement of both proliferation and IFN-gamma release in the mixed lymphocyte reaction (MLR). BMS has found that using a CMV-re-stimulation assay with human PBMC, the effect of nivolumab on antigen-specific recall response indicates that nivolumab augmented IFN-gamma secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).

4.4.2 Pharmacodynamics

Please see Clinical Pharmacology review. In study 063, there was no significant Exposure-Response (ER) relationship for nivolumab at 3 mg/kg when analyzing Cmin and ORR. In addition, no E-R relationship for safety was observed when analyzing Cavg and Grade 3+ drug-related AEs at doses ranging from 0.1 to 10 mg/kg in a pooled analysis.

4.4.3 Pharmacokinetics

Single dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in study CA209001, whereas multiple dose PK is being evaluated in subjects in study CA209003. BMS states that, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~350 subjects from CA209001, CA209002, and CA209003. Single dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median T_{max} 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 C_{max} and $AUC_{(INF)}$ with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) 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 T-1/2 of nivolumab is 17 to 25 days, which is consistent with the half-life of endogenous IgG4, suggesting that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from studies CA209001, CA209002 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights.

5 Sources of Clinical Data

This sBLA includes 2 clinical study reports and data (CA209063 and CA209003). Study CA209063 is the pivotal phase 2 single arm study conducted in refractory squamous NSCLCA. Study CA209003 (located under the rolling BLA125554) is a supportive, safety and dose finding phase 1 study conducted in various solid tumors. In addition, legacy data and a DMC report from study CA209017 was submitted. This was a randomized second-line squamous NSCLC study which is currently ongoing. Data from this study during the interim DMC analysis was fairly mature and therefore submitted and critical for a risk-benefit determination for this application. Safety results were also submitted from melanoma Study CA209037.

Data from the pivotal study, CA209063 in addition to the interim results analyzed by the DMC for the primary endpoint of overall survival from study CA209017 serves as the primary basis for evaluation of efficacy and safety.

5.1 Tables of Studies/Clinical Trials

Table 6: Key Clinical Studies submitted and used for evaluation of this supplement **(Source: BLA 125527; Reviewer Table)**

Study	Design	Cancer	Regimen	Number	Comments
CA209017	Phase 3, randomized standard of care Docetaxel vs. Nivolumab after 1st line doublet chemo therapy	Advanced, Squamous NSCLC	Nivolumab 3 mg/kg IV every 2 weeks Docetaxel 75 mg/m^2 IV every 3 weeks	272	Key study for this supplement. Results based on DMC analysis of interim OS results; Ongoing
CA209063	Phase 2, single arm, >2 prior lines of therapy	Advanced, Squamous NSCLC	Nivolumab 3 mg/kg IV every 2 weeks	117	Pivotal Phase 2 study for this supplement, study completed

Table 7: Additional Submitted Studies (Source: BLA 125527; Reviewer Table)

Study	Design	Cancer	Regimen	Number	Comments
CA209003	Dose escalation, multi- cohort safety, tolerability, and recommended Phase 2 dose Phase 1 study	Metastatic NSCLC, colorectal cancer, melanoma, renal cell cancer, or castrate resistant prostate cancer	Nivolumab 0.1, 0.3, 1, 3, or 10 mg/kg every 2 weeks for treatment up to 2 years	306	
CA209037	Phase 3, randomized open label study of nivolumab vs. investigator's choice	Advanced, ALK +, NSCLC	Randomized 2:1 to: Nivolumab - 3 mg/kg IV every 2 weeks Investigator's choice – DTIC 1000 mg/m^2 IV every 3 weeks or carboplatin (AUC 6) IV and pacletaxel 175mg/m^2 every 3 weeks	370	Ongoing; Only safety data submitted

5.2 Review Strategy

The clinical review is based on the clinical study report for the pivotal study CA209063 and supplemented with the DMC analysis of the key study CA209017. Both safety and efficacy conclusions were drawn from Study CA209063 and efficacy conclusions were drawn from Study CA209017. The clinical study reports, DMC reports, supportive analyses and risk:benefit assessment submitted by the applicant were reviewed. Key safety and efficacy datasets were re-analyzed by the clinical and statistical reviewers. The efficacy review for the above two studies was conducted by Dr. Dickran Kazandjian and the safety review of study CA209063 was conducted by Dr. Sean Khozin. Both safety and efficacy were additionally reviewed by Dr. Gideon Blumenthal. A statistical review was conducted by Dr. Lijun Zhang and reviewed by Dr. Shenghui Tang. Among the items reviewed were the case report forms, selected narratives, primary data sets for baseline characteristics, efficacy and toxicity submitted by the applicant. The reliability of the data were assessed based on information obtained from the conflict of interest data, protocol deviations and via random cross-validation of datasets with CRF forms. Sensitivity analyses and subgroup analyses were performed as necessary. Additionally, FDA's "Jump Start" service was used to evaluate the technical integrity of Study CA209063's data set (SDTM) and conformity to CDISC.

5.3 Discussion of Individual Studies/Clinical Trials

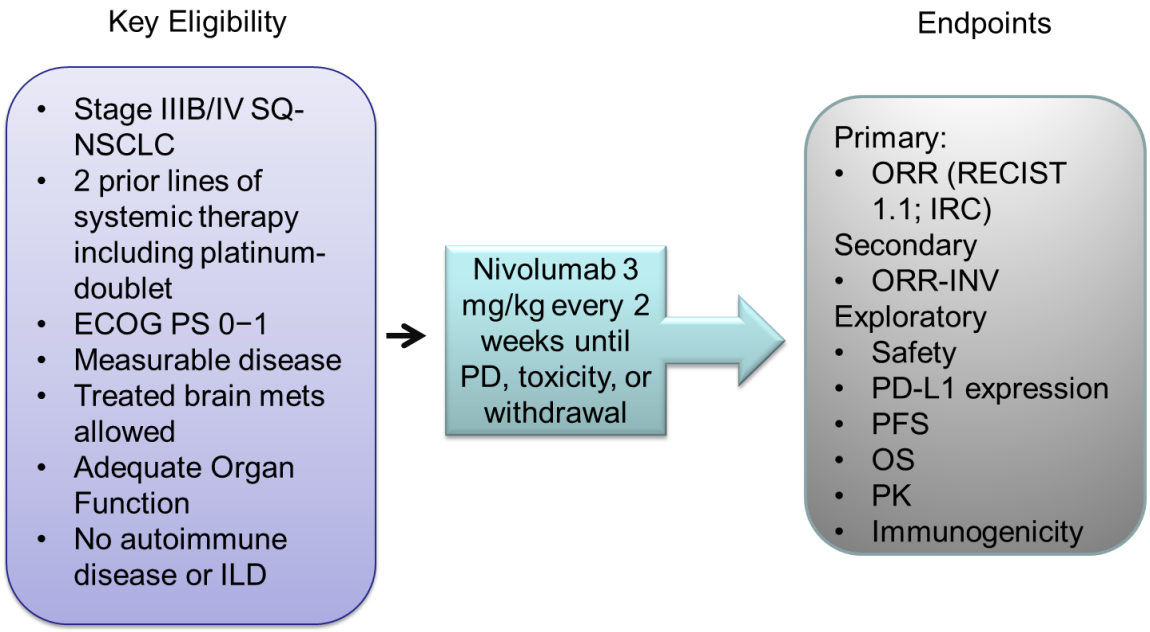
5.3.1 Phase 2 Trial CA209063

This sBLA submission is primarily supported by the results of the industry-sponsored trial titled:

A Single-Arm Phase 2 Study of Nivolumab (BMS-936558) in Subjects with Advanced or Metastatic Squamous Cell Non-Small Cell Lung Cancer Who Have Received at Least Two Prior Systemic Regimens

CA209063 design and treatment plan:

Figure 9: study design



This was a single-arm Phase 2 study of nivolumab in adults (aged ≥18 years) with locally advanced or metastatic SQ NSCLC who had progressed during or after both platinum doublet-based chemotherapy and at least 1 additional systemic therapy in the advanced/metastatic setting. The design was as an open-label, single-arm trial with patients receiving 3 mg/kg nivolumab as an IV infusion over 60 minutes every 2 weeks. A maximum dose delay of 6 weeks was allowed. Each cycle consisted of 2 weeks and treatment was continued until disease progression, or discontinuation of study therapy in subjects receiving nivolumab beyond progression (see below), discontinuation due to toxicity, or other reasons for discontinuation as defined in the protocol. Treatment beyond progression was allowed in subjects who were tolerating study drug and experiencing clinical benefit as assessed by the investigator.

The study consisted of 3 phases: screening, treatment, and follow-up.

Screening Phase: Eligibility of subjects was determined during the screening process.

Treatment Phase: In the treatment phase, nivolumab was administered on Day 1 of each 2-week cycle. Subjects were assessed for tumor response, safety, PK, biomarkers, and immunogenicity. Tumor responses were assessed by the independent radiology committee (IRC) and investigator using RECIST v1.1 criteria. The primary endpoint was confirmed ORR, as assessed by the IRC, according to RECIST v1.1 criteria. Radiographic assessments of tumor response were performed at Week 8 (+/- 5 days) and every 6 weeks after Week 8 (+/- 5 days) until disease progression (or discontinuation of study therapy in subjects receiving nivolumab beyond initial progression) or other protocol-defined reasons.

Follow-Up Phase: The follow-up phase began when subjects were discontinued from study therapy. Two follow-up visits within the first 100 days from the last dose of study therapy included safety assessments and collection of PK and immunogenicity samples. Thereafter, subjects were followed for AEs or serious adverse events (SAEs) whether related or not related to study drug for a minimum of 100 days after last dose of study drug, or until these resolved, returned to baseline, or were deemed irreversible. In addition, any serious adverse events (SAEs) related to study drug (or associated with protocol-specified procedures) that occurred after 100 days from the last dose of study therapy were to be reported by the investigator. Subjects who discontinued study therapy for reasons other than disease progression and subjects treated beyond progression had radiographic tumor assessments every 6 weeks (+/- 5 days) until documented disease progression or further progression. Beyond the 2 protocol-scheduled follow-up visits, subjects were followed every 3 months for survival.

In an exploratory fashion, the potential association between efficacy and safety endpoints and expression of PD-L1 protein as measured in tumor tissue was evaluated. Pre-study (baseline) tumor tissues (archival or recent acquisition, formalin-fixed, paraffin-embedded tumor tissue block or unstained slides) were systematically collected in all subjects, when available, for determination of baseline PD-L1 expression status. CA209063 will end when analysis of survival is completed, up to 5 years beyond analysis of the primary endpoint. At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug.

Dose escalation or reduction was not permitted. The protocol allowed for administration of nivolumab to be delayed based on occurrence of certain AEs and their grade, laboratory value abnormalities, or intercurrent illness. The criteria for dose delay and for subsequent resumption or for discontinuation of treatment are specified.

Study Objectives:

Primary Objective:

- To assess the clinical activity of nivolumab, as measured by the independent radiology review committee (IRC) -assessed objective response rate (ORR), in subjects with advanced or metastatic squamous cell NSCLC who have progressed during or after both platinum doublet based chemotherapy and at least one additional systemic therapy

Secondary Objective(s):

- To estimate the ORR based on investigator assessment of response

Exploratory Objective(s):

- To assess the overall safety and tolerability of nivolumab, as measured by incidence and severity of adverse events and specific laboratory abnormalities
- To evaluate potential association between PD-L1 expression and efficacy endpoints
- To estimate the progression-free survival (PFS) of nivolumab in all treated subjects
- To estimate the overall survival (OS) of nivolumab in all treated subjects
- To characterize pharmacokinetics of nivolumab and explore exposure-response (exposure-safety and
- exposure-efficacy) relationships with respect to selected safety and efficacy endpoints
- To characterize immunogenicity of nivolumab

Eligibility Criteria

Subjects of either sex, at least 18 years of age, who signed the Informed Consent Form and who met the following main disease criteria upon screening were to be included in the study:

Inclusion:

- Histological or cytological confirmation of SQ NSCLC (stage IIIB/ stage IV disease according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology) or recurrent or progressive disease (PD) following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease)
- Disease progression or recurrence experienced after both a platinum doublet-based chemotherapy regimen and at least 1 additional systemic therapy, given as monotherapy or in combination; or vinorelbine- or gemcitabine-containing

regimens given as part of locally accepted standard-of-care, for subjects who are not candidates for docetaxel
    - Maintenance therapy following platinum doublet-based chemotherapy was not considered as a separate regimen of therapy.
    - Prior platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease was considered first-line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Subjects with recurrent disease > 6 months must also have progressed after a subsequent platinum-based regimen given to treat the recurrence.
    - Subjects with activating epidermal growth factor receptor (EGFR) mutations were allowed to have received an EGFR tyrosine kinase inhibitor (TKI) prior to platinum-based chemotherapy.
- Measurable disease by computerized tomography (CT) or magnetic resonance imaging (MRI) per RECIST v1.1 criteria, with radiographic tumor assessment performed within 28 days of first dose of study drug.
- Target lesions may have been located in a previously irradiated field if there was documented (radiographic) disease progression in that site.
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤1
- Prior radiotherapy or radiosurgery completed at least 2 weeks prior to first dose of study drug.
- Screening laboratory values must meet the following criteria:
    - WBCs ≥ 2000/μL
    - Neutrophils ≥ 1500/μL
    - Platelets ≥ 100 x 10^3/μL
    - Hemoglobin ≥ 9.0 g/dL
    - Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)
    - AST ≤ 3X ULN
    - ALT ≤ 3X ULN
    - Total bilirubin ≤ 1.5X ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)
- Women of childbearing potential must use method(s) of contraception based on the tables in Appendix 2 of the protocol. The individual methods of contraception and duration should be determined in consultation with the investigator. When the half-life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half-lives.
- Men who are sexually active with child bearing potential women must use any contraceptive method with a failure rate of less than 1% per year. The investigator shall review contraception methods and the time period that contraception must be followed. Birth control should continue as long as the half-life of the investigational drug is greater than 24 hours, contraception should be

continued for a period of 90 days plus the time required for the investigational drug to undergo five half-lives.

Exclusion Criteria:

- Target Disease Exceptions:
  - Subjects with untreated CNS metastases are excluded. Subjects are eligible if CNS metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
  - Subjects with carcinomatous meningitis.
- Medical History and Concurrent Diseases
  - Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
  - 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, inhalational), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
  - Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
  - Prior treatment on either arm of nivolumab study CA209017 or ipilimumab study CA184104.
  - Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
  - Other active malignancy requiring concurrent intervention.
  - Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
  - All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.
  - Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study treatment.

    - Prohibited Treatments and/or Restricted Therapies:
        - Ongoing or planned administration of anti-cancer therapies other than those specified in this study
        - Use of corticosteroids or other immunosuppressive medications
        - Anti-cancer therapy, including an investigational agent, less than 14 days prior to the first dose of study drug
- Physical and Laboratory Test Findings
    - Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
    - Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection
- Allergies and Adverse Drug Reaction
    - History of severe hypersensitivity reactions to other monoclonal antibodies.
    - History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.
- Sex and Reproductive Status
    - Women of child bearing potential who are pregnant or breastfeeding.
    - Women with a positive pregnancy test at enrollment or prior to administration of study medication.
- Other Exclusion Criteria
    - Any other serious or uncontrolled medical disorder, active infection, physical exam finding, laboratory finding, altered mental status, or psychiatric condition that, in the opinion of the investigator, would limit a subject's ability to comply with the study requirements, substantially increase risk to the subject, or impact the interpretability of study results.
    - Prisoners or subjects who are involuntarily incarcerated.
    - Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Criteria for Patient Discontinuation from Study or Therapy

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Subject's request to stop study treatment (withdrawal of informed consent).
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
    - Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment.
    - Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions:

        - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 5-10x ULN for > 2 weeks
            - AST or ALT > 10x ULN
            - Total bilirubin > 5x ULN
            - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
- Any dosing interruption lasting > 6 weeks with the following exceptions:
    - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
    - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.
- Pregnancy.
- Termination of the study by Bristol-Myers Squibb.
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
- Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further

contact with him/her or persons previously authorized by subject to provide this information.

Treatment Agents

Nivolumab at 3 mg/kg was administered as an IV infusion over 60 minutes on Day 1 of each 2-week cycle using a volumetric pump with a 0.2/0.22 micron in-line filter. Dosing calculations were based on the subject's body weight assessed at each visit. Subjects received nivolumab 3 mg/kg until disease progression (or discontinuation of study therapy in subjects receiving nivolumab beyond progression), discontinuation due to toxicity, or other protocol-specified reasons. Nivolumab, was formulated at a concentration of 10 mg/mL and supplied to the study sites in 10-mL vials containing 10 mL of drug product. The drug product is a sterile solution for parenteral administration. Nivolumab batches administered to patients were 2A73820, 2E71978, 2H62312, 2M50921, and 3C83433.

Treating beyond RECIST progression:
Given preliminary knowledge of immune therapies, a few patients may benefit in the long run despite early progression. Therefore, patients were allowed to be treated past progression as long as they met the following criteria:

- Investigator-assessed clinical benefit, and did not have rapid disease progression
- Tolerance of study drug
- Stable performance status
- Treatment beyond progression would not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provided written informed consent prior to receiving additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.
- For patients who continued nivolumab beyond progression, further progression was defined as an additional 10% increase in tumor burden volume from time of initial progression. This included an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment was to be discontinued permanently upon documentation of further disease progression.

The decision to continue treatment beyond initial progression was discussed with the BMS medical Monitor and documented in the study records. A radiographic assessment/ scan was to be performed within six weeks of original progressive disease to determine whether there was a decrease in the tumor size, or continued PD. The assessment of clinical benefit was to be balanced by clinical judgment as to whether the subject was clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab. If the investigator felt that the nivolumab subject continued to achieve clinical benefit by continuing treatment, the subject would remain on the trial and continue to receive monitoring according to the schedule.

Dose Modifications and Management of Toxicities:

The monotherapy dose and schedule of nivolumab 3 mg/kg every two weeks was selected for Phase 2/3 studies based on an integrated assessment of nivolumab data from in vitro and preclinical studies, as well as clinical PK, safety, and efficacy results from 2 Phase 1 studies (MDX1106-01 and CA209003). The majority of the clinical efficacy and safety data supporting the selection of 3 mg/kg every 2 weeks was from CA209003 which was a multiple-ascending-dose study designed to characterize the safety, tolerability, PK, pharmacodynamics and anti-tumor activity of nivolumab monotherapy in subjects with relapsed or refractory advanced or recurrent malignancies. Clinical activity was detected in subjects with NSCLC, melanoma and renal cell carcinoma (RCC), and therefore the study was amended to expand the safety and anti-tumor experience in these tumor types at various dose levels ranging from 0.1 to 10 mg/kg Q2W. A total of 306 subjects were treated. Specific clinical findings among the 129 NSCLC subjects treated that contributed to the selection of the Phase 2/3 dose were as follows:

- A greater percentage of objective responses were observed in NSCLC subjects treated with 3 mg/kg (24.3%) and 10 mg/kg (20.3%) than with 1 mg/kg (3.0%) nivolumab.
- Similar ORRs were observed across squamous and non-squamous NSCLC histologies at all dose levels.
- In exposure-response analysis, the probability of response in NSCLC subjects increased over the range of steady-state trough concentrations observed, but appeared to plateau at the ≥ 3 mg/kg every 2 week dose.

The nature, frequency and severity of drug-related AEs (including pulmonary select AEs), SAEs, AEs leading to discontinuation, and deaths were similar in NSCLC subjects across dose levels and histologies, as compared to the overall study population. Dose modifications of nivolumab were not allowed.

Subjects were allowed to resume treatment with nivolumab when the drug-related AE resolved to Grade ≤ 1 or baseline, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5.1) should have treatment permanently discontinued.

- Drug-related pulmonary toxicity, diarrhea, colitis or nephritis must have resolved to baseline before treatment is resumed. Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy.

Treatment of Nivolumab-Related Infusion Reactions

Nivolumab is a humanized antibody and therefore predicted to rarely induce hypersensitivity or infusion reactions which are manifested by fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions were to be reported within 24 hours to the study medical monitor and reported as an SAE if it met the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines. Treatment recommendations were provided in the protocol to include:

- Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated):
    1. Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.
- Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti- inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):
    1. Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit.
    2. For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
- For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated

for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life-threatening; pressor or ventilatory support indicated).

1. Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

Study Assessments:

The following assessments were to be monitored starting on Cycle 1 Day 1 and as stated in the schedule of assessments.

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest within 72 hours of dosing. Obtain prior to dosing and at any time a subject has any new or worsening respiratory symptoms. If a subject shows changes in oxygen saturation or supplemental oxygen requirement, or other pulmonary-related signs (eg, hypoxia, fever) or symptoms (eg, dyspnea, cough) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity, according to the suspected pulmonary toxicity management algorithm contained within the Investigator's Brochure.
- AEs continuously throughout the study.
- Physical examination and physical measurements including weight, and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose and LDH): results to be obtained prior to dosing on infusion days.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results to be obtained prior to dosing on infusion days).
- Thyroid function testing includes TSH (reflex to free T3 and free T4 if abnormal result).
- Pregnancy test for WOCBP will be performed every 6 weeks on study or more frequently as per local standard.

Statistical Plan:

Sample Size:
The study was planned to treat approximately 100 subjects. The maximum width of the exact 2-sided 95% confidence interval (CI) is 20% when the ORR is expected to be in the 10% to 50% range.

Analysis Populations:

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All Treated Subjects: All subjects who received at least one dose of nivolumab. This is the primary population for safety and efficacy analyses.
- All response evaluable subjects: All subjects who have baseline and at least one on-study evaluable tumor measurements.
- PK subjects: All subjects with available serum time-concentration data from subjects dosed with nivolumab.
- Immunogenicity subjects: all treated subjects with available immunogenicity data.
- PD-L1 measurable subjects: all treated subjects with a measurable PD-L1 expression result.

The primary objective was to measure the primary endpoint of IRC assessed ORR. It is defined as the number of subjects with a best overall response (BOR) of confirmed CR or PR divided by the number of treated subjects. Tumor assessments were to occur 8 weeks (+/- 5 days) after treatment begins and continue every 6 weeks (=/- 5 days) until disease progression (discontinuation of study therapy in patients receiving nivolumab beyond progression), lost to follow-up, or withdrawal of study consent .This analysis was to occur at least 6 months after the last enrolled subject's first dose of study treatment. Best overall response (BOR) was defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression per RECIST v1.1 or the date of subsequent therapy, whichever occurred first. For subjects without documented progression or subsequent therapy, all available response designations would contribute to the BOR determination. Objective response would be further characterized by the duration of response (DOR). DOR was defined as the time from first confirmed response (CR or PR) to the date of the initial objectively documented tumor progression as determined using RECIST 1.1 criteria or death due to any cause, whichever occurred first. For subjects who neither progressed nor died, the DOR would be censored on the date of their last evaluable tumor assessment. DOR would only be evaluated in subjects with objective response of CR or PR.

The ORR was to be summarized by binomial response rates and their corresponding two-sided 95% exact CIs using Clopper-Pearson method. The assessed DOR was to be summarized for subjects who achieved confirmed PR or CR using the Kaplan-Meier

(KM) product-limit method. Median values of DOR, along with two-sided 95% CI using Brookmeyer and Crowley method, were also to be calculated. In addition, the percentage of responders still in response at different time points (3, 6 and 12 months) was to be presented based on the DOR KM plot.

Safety Analyses:
Safety was to be summarized and listed for all treated subjects using the NCI CTCAE version 4.0. All on-study AEs, drug-related AEs, SAEs and drug-related SAEs were tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function, and renal function were summarized using worst grade per NCI CTCAE v4.0 criteria.

PK and Biomarker Analyses:
Serum samples were to be collected to characterize pharmacokinetics of nivolumab and to explore exposure-safety and exposure-efficacy relationships. A variety of factors that may impact the immunomodulatory properties and efficacy of nivolumab were to be investigated in peripheral blood, and in tumor specimens taken from all subjects as specified.

Changes to the Protocol:
The original protocol was amended 6 times.

Table 8:Important Study CA209063 Protocol Amendments

Amendment#	Version Date	Summary of Changes
6	16 May 2013	• Per request of the German Health Authority (PEI), changed exclusion criteria to require screening brain MRI in all subjects and to clarify requirement for on-study follow-up brain MRI scans • Added "MRI of the Brain" assessment to Radiographic Tumor Assessments at screening for all subjects enrolled in Germany
4	28 March 2013	• Modified the primary objective of the trial to ORR as assessed by an IRC; and subsequently modified the secondary objective to ORR as assessed by the investigator • Replaced or added " the generic name "nivolumab" to BMS-936558 • Additionally identified the clinical trial protocol CA209063 as "CheckMate 063: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 063" • Updated recommendations to clinically manage subjects with opportunistic infections due to prolonged high-dose corticosteroid administration. • Clarified the target population and allowable therapies, and updated the protocol with additional clarifications and typographic revisions. • The exclusion criteria for central nervous system metastases was modified from the original protocol language stating exclusion of active brain metastases, to clarify that any untreated brain metastases were excluded
2	11 Jan 2013	• Per request of the Competent Health Authority in France, recommended management algorithms for suspected pulmonary toxicity, diarrhea/colitis, suspected hepatotoxicity, suspected endocrinopathy and nephrotoxicity, which were previously located only in the Investigator Brochure, were added as a protocol appendix. References to the safety management guidelines in the appendix were added to the protocol text..

Changes to the Statistical Analysis Plan (SAP)

The SAP was amended once and included the following major changes:

Major changes:

- Primary analysis of BOR per IRC: definition of endpoint clarified. ORR by subset analysis added. Time to response analyses added. ORR sensitivity analyses added. Subject-level graphics added
- Secondary endpoint ORR per investigator: time to response analysis added
- PFS rates per IRC at fixed time points added.
- Duration of stable disease per IRC added
- Duration of response: censoring rules clarified
- OS/ ORR analyses by subsets: following subsets added: region, age category ≥65 - < 75, number of prior therapies, time from most recent prior regimen to start of treatment
- Section for analysis of extent and currentness of follow up for survival revised
- PD-L1 expression: definition of PD-L1 endpoint, definition of population for analysis, and list of analyses revised.

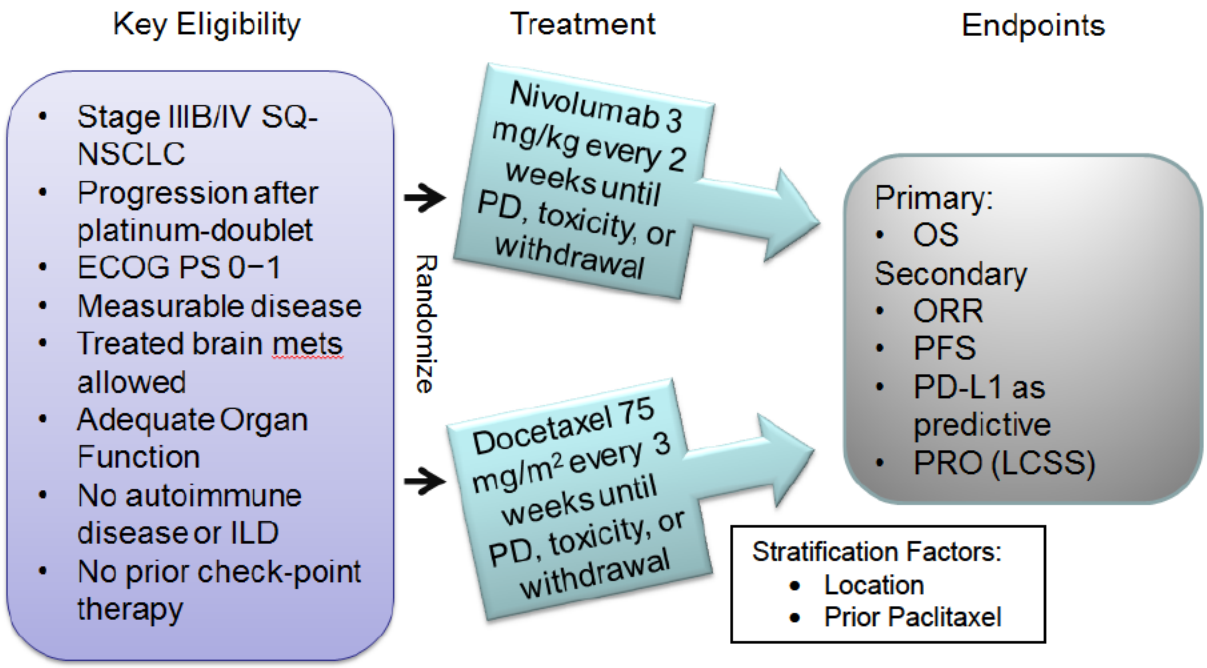
5.3.2 Phase 3 Trial CA209017

This sBLA submission is additionally supported by the results of the industry-sponsored trial titled:

An Open-label Randomized Phase III Trial of BMS-936558 (Nivolumab) versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)

Study design: This is an open-label, randomized, Phase 3 study in adult (≥ 18 years old) male and female subjects with advanced or metastatic squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy. Approximately 272 subjects were to be randomized to BMS-936558 (nivolumab) vs docetaxel in a 1:1 ratio. Subjects underwent screening evaluations to determine eligibility within 28 days prior to randomization. Subjects were assigned to one of two treatment arms. Randomization was stratified and balanced according to the following factors of prior paclitaxel vs. no paclitaxel and region (US vs Europe vs Rest of World). For subjects randomized to nivolumab, it was dosed intravenously over 60 minutes at 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity or other reasons specified in the protocol. For subjects randomized to Docetaxel, they were dosed intravenously over 60 minutes at 75mg/ m^2 every 3 weeks until disease progression, unacceptable toxicity or other reasons specified in the protocol.

Figure 10: Study design



Study Objectives: The primary objective was to compare the OS of nivolumab versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy. The secondary objectives included the comparison of ORR for nivolumab versus docetaxel, comparison of PFS of nivolumab versus docetaxel, the evaluation of whether PD-L1 expression is a predictive biomarker for OS, ORR, or PFS, and the evaluation of the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks, as measured by LCSS in nivolumab and docetaxel groups.

Key Inclusion Criteria:

- Men and women ≥ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
- Subjects with histologically- or cytologically-documented squamous cell NSCLC who present with Stage IIIB/ Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced disease).

- Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.
    - Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.
    - Subjects who received platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, and developed recurrent (local or metastatic) disease within 6 months of completing therapy are eligible.
    - Subjects with recurrent disease > 6 months after platinum-containing adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum doublet-based regimen given to treat the recurrence, are eligible.
- Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization
    - Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site
- A formalin-fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.

Key Exclusion Criteria:

- Subjects with untreated CNS metastases are excluded. Subjects are eligible if CNS metastases are treated and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent).
- Subjects with carcinomatous meningitis
- Subjects with active, known or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Prior treatment on the first-line study CA184104
- Prior treatment with docetaxel
- Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
- Other active malignancy requiring concurrent intervention
- Subjects with previous malignancies (except non-melanoma skin cancers, and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, melanoma, or breast) are excluded unless a complete remission was achieved at least 2 years prior to study entry AND no additional therapy is required during the study period
- All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.
- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least s14 days before the first dose of study treatment
- Treatment with any investigational agent within 14 days of first administration of study treatment.

Statistical Plan

The study was designed to target a 7 month median OS time for docetaxel-treated patients and an overall 8.9 month median OS time for nivolumab-treated patients based on a piecewise mixture of non-proportional hazards for nivolumab (4 months with no separation of the curves and a 18% “cure” rate along with a 7.9 month median OS time for non-“cured” patients). Based on the above piecewise mixture model assumptions, the hazard ratio between nivolumab and docetaxel arm would follow the following pattern: Months 0-4: HR=1; Month 6: HR=0.63; Month 12: HR=0.51; Month 24: HR=0.28; Month 36: HR=0.13. At least 231 deaths among the 272 randomized patients were required to provide 90% power to detect the targeted differences above at an alpha level of 5% (two-sided). One interim analysis was scheduled at 85% information. Lan-DeMets alpha spending method of the O’Brien-Fleming boundary was employed to control the overall alpha level.

If superiority in OS was to be demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints would be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints to be tested in the following hierarchical order were:
1.) ORR
2.) PFS

The formal statistical testing for ORR was to take place only if OS was statistically significant and the statistical testing for PFS was to take place only if both OS and ORR were statistically significant.

The distribution of OS was to be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by prior paclitaxel use and region as entered into the IVRS. The hazard ratio (HR) and confidence interval (CI) were to be estimated in a stratified Cox proportional hazards model. The OS curves for each randomized arm were to be estimated using the Kaplan-Meier (KM) product limit method. Two-sided, 95% confidence intervals for median OS was to be computed by Brookmeyer and Crowley method (using log-log transformation). The comparison of ORR was to be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by the above factors. An associated odds ratio and 95% CI was to be calculated. ORR and their corresponding 95% exact CI was to be calculated by the Clopper-Pearson method for each randomized arm. Summary statistics of time to objective response (TTR) was to be provided for each treatment group for subjects who achieved a PR or CR. Duration of response (DOR) in each treatment group was to be estimated using the KM product-limit method for subjects who achieved a PR or CR. Median values along with two-sided 95% CI was to be calculated. The distribution of PFS was to be compared between the two randomized groups using a two-sided, log-rank test stratified by prior use of paclitaxel vs. no paclitaxel use, and by region (US vs Europe vs Rest of World). HR and corresponding two-sided 95% CI were to be estimated in a stratified Cox proportional hazards model. The PFS curves for each treatment group were to be estimated using the KM product-limit method. Two sided, 95% confidence intervals for median PFS was to be computed by the Brookmeyer and Crowley method. Other secondary endpoints included PD-L1 expression as a predictive biomarker for efficacy endpoints and a disease related symptom progression rate.

Changes to the Protocol:
The original protocol was amended 9 times.

Table 9: Important Study CA209063 Protocol Amendments

Amendment#	Version Date	Summary of Changes
9	25 April 2014	• Modification to the overall survival (OS) analysis for CA209017 Modification to move objective response rate from a co-primary endpoint to a secondary endpoint (OS remains as the sole primary endpoint).
7	29 May 2014	• The approved generic name "nivolumab" for BMS-936558 was added throughout the document
6	March 8 2013	• Safety Summary was updated to include language on preliminary new non-clinical safety findings of adverse pregnancy outcomes

5.3.3 Phase 1 Trial CA209003

Study design: CA209003 was a Phase 1, open-label, multicenter, multi-dose, dose-escalation study of nivolumab. The study consisted of 3 periods: Screening (up to 28 days), Treatment (up to 3 years of active therapy [up to a maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurred. Each treatment cycle comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43 with a response assessment between Days 52 and 56. The response assessment must have been completed before the first dose in the next cycle. Subjects entering the follow-up period with ongoing disease control (ongoing CR, PR, or SD) may have been permitted to reinitiate study therapy upon confirmed disease progression after discussion and agreement with the BMS Medical Monitor. Following completion of the treatment and follow-up periods, all subjects were followed for survival.

Objectives: The primary objective was to assess the safety and tolerability of multiple doses in subjects with selected advanced or recurrent malignancies. The malignancies include: metastatic castration-resistant prostate cancer (mCRPC), RCC, colorectal adenocarcinoma (CRC), malignant melanoma (MEL), and NSCLC. The secondary objectives were to: 1) assess the host immune response (immunogenicity); 2) characterize the pharmacokinetic profile of multiple doses; 3) assess the preliminary efficacy of monotherapy; 4) to characterize the dose response relationship in melanoma and in NSCLC; and 5) explore the effects on humoral and cellular immune responses to tumor antigens and recall responses to a panel of non-tumor antigens. Exploratory objectives were 1) To explore potential predictive markers associated with clinical activity based on levels of expression of PD-L1 in tumor specimens prior to treatment; 2) to investigate the immunomodulatory activity on selected immune cell populations and soluble factors in blood; 3) to characterize the level of PD-1 receptor occupancy in peripheral blood; 4) to assess the overall survival in subjects receiving nivolumab.

Treatment plan: Three dose levels are planned: 1, 3, and 10 mg/kg and additionally 0.1 mg/kg and 0.3 mg/kg dose levels were added as part of Amendment 4 to the protocol. Subjects will be assigned to a dose level in the order of study entry. Initially, 3 subjects will be enrolled at the 1 mg/kg dose level and follow a standard 3+3 design.

Expansion Cohorts: To further characterize safety and efficacy, up to 14 expansion cohorts will be enrolled. Accrual to 7 expansion cohorts has completed; an additional 7 expansion cohorts will be enrolled under Amendment 4. A total of 6 subjects must be enrolled at the MTD (or the highest dose studied where ≤ 1 of 6 subjects experiences a DLT if the MTD is not identified) and evaluated through the end of Cycle 1 before any new subject is dosed in the expansion cohorts. If none of the first 5 subjects have a DLT by the end of Cycle 1, enrollment to the primary expansion cohorts can begin immediately following enrollment of the sixth subject. Up to 7 expansion cohorts will be enrolled (enrollment to these expansion cohorts has completed) and an additional 7

more including 3 NSCLC cohorts at the doses of 1, 3, and 10 mg/kg. Tumor response will be evaluated using RECIST with modifications. End of cycle tumor response assessments for all subjects will occur within Days 52 to 56 (results of assessments must be reviewed and documented before the first dose of the next cycle). The maximum duration of study therapy to be administered to an individual subject in this study is 3 years (up to maximum of 2 years of initial treatment plus additional remaining period if re-initiation of study therapy occurs). Following each treatment cycle, the decision to treat a subject with additional cycles will be based on tumor assessment (evaluation performed between Days 52 and 56 and before the first dose in the next cycle). No subject will be permitted dose escalations or de-escalations with the exception of subjects with melanoma enrolled in the 0.1 mg/kg or 0.3 mg/kg additional expansion cohorts who meet the criteria for dose escalation as outlined above; dose adjustments are allowed only if there has been a 10% or greater change in weight (increase or decrease) since the previous cycle.
Subjects who meet the following conditions may be treated with additional cycles:

1. Subjects with a best overall response of complete response, partial response or stable disease will receive treatment until the first occurrence of either:
    a. achievement of a confirmed CR
    b. clinical deterioration suggesting that no further benefit from treatment is likely
    c. meets criteria for discontinuation of study therapy due to DLTs
    d. other intolerability to therapy
    e. receipt of the maximum number of cycles
2. Subjects with PD that has been confirmed but is not worsening and with otherwise stable or improved clinical status should continue to be treated with study drug until there is further progression or clinical deterioration.

Statistics: Up to 290 subjects were initially planned to be enrolled. Under Amendment 4 approximately 160 additional subjects will be enrolled. Subjects with pathologically-verified mCRPC, RCC, CRC, MEL, or NSCLC that is clinically advanced or recurrent and progressing after prior treatment with other therapies, and for which no alternative curative option is available, will be eligible to enroll in the study. Only subjects with RCC, MEL, or NSCLC will be enrolled under Amendment 4.

The sample size during dose escalation was based on observed toxicity. At expansion cohorts, up to 16 or 32 subjects were to be treated at fixed doses in a tumor type, to provide preliminary assessment of tumor response, in addition to safety assessment. With 16 subjects treated in an expansion cohort, at a fixed dose and tumor type the 90% confidence interval for an objective response rate would be (5.3% to 42%) if 3 (19%) subjects had a response, (9.0% to 48%) if 4 (25%) subjects had a response and (13.2% to 54.8%) if 5 (31%) subjects had a response. Similarly, with 32 subjects in each NSCLC expansion cohort, the 90% confidence interval for an objective response rate would be (3% to 22%) if 3 (9.4%) subjects had a response, (4.4% to 26.4%) if 4 (12.5%) subjects had a response, and (6.4%, 30%) if 5 (16%) subjects had a response.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

BMS proposed the following indication in their sBLA submission:

"OPDIVO is a (b) (4) *programmed death receptor-1 (PD-1) blocking antibody indicated for the treatment of patients with* (b) (4) *squamous non-small cell lung cancer* (b) (4)

6.1.1 Methods

This review will focus primarily on the efficacy results from a randomized phase 3 trial (CA209017) and a single arm phase 2 trial (CA209063) evaluating the efficacy of nivolumab in the 2nd and 3rd line treatment in SQ NSCLC. For further information on the study design, see section 5.3.1-2. The efficacy review incorporates the statistical review, conducted by Dr. Zhang and the clinical review conducted by Dr. Kazandjian.

PREAMBLE:

The single arm trial (CA209063) was the sponsor's original focus for the submission with the primary endpoint of ORR to support accelerated approval. However, the results of the trial in itself was not compelling to reasonably predict clinical benefit. At the time of submission, BMS's phase 3 trial (CA209017) underwent a pre-specified interim analysis review by a blinded independent data monitoring committee (DMC). Based on BMS' request, (b) (4) prepared a report for the FDA with a subset of the information related to the formal interim comparison of overall survival. The DMC Charter specified that this formal interim OS analysis was to be performed when at least 196 deaths (85% of the total 231 deaths) had been observed and the report was based on 199 deaths. The DMC unanimously recommended the un-blinding of the study since the pre-specified boundary was crossed and noted no concerning safety signal. The study was subsequently amended to allow crossover of patients from the control to the nivolumab arm. The DMC's analysis of the primary endpoint of OS was very compelling and FDA considered the DMC results from this trial as the basis for traditional approval.

STUDY CA209017:

6.1.2_CA209017 Demographics

Table 10: Summary Characteristics for Trial CA209017 (Source: CA209017 dataset/study report; Reviewer Table)

Demographic		*Nivolumab (n=135)*	*Docetaxel (n=137)*	*Total (n=272)*
Age (years)	Mean	62	64	63
	Median	62	64	63
	Range	39-85	42-84	39-85
Sex	Male	82.2%	70.8%	76.5%
Race	White	90.4%	94.9%	92.6%
	Black	4.4%	1.5%	2.9%
	Asian	3.0%	1.5%	2.2%
	Other	0.7%	1.5%	1.1%
Smoking	Current/former	89.6%	94.2%	91.9%
	Never	7.4%	5.1%	6.3%
Histology	Squamous	98.5%	100%	99.3%
Extent	Stage IIIB	21.6%	17.6%	19.6%
	Stage IV	78.4%	82.4%	80.4%
ECOG PS	0	20.0%	27.0%	23.5%
	1	78.5%	73.0%	75.7%
Brain	Metastasis	6.7%	5.8%	6.3%
Paclitaxel	Prior use	34.1%	33.6%	33.8%
Number of prior regimens	1st Line	99.3%	100%	99.6%
Received 1st line platinum doublet	% of patients	100%	100%	100%

Reviewer Note: The two arms of the trial were fairly well balanced. The trial as a whole was weighted towards males.

Study locations for the trial included many diverse countries.

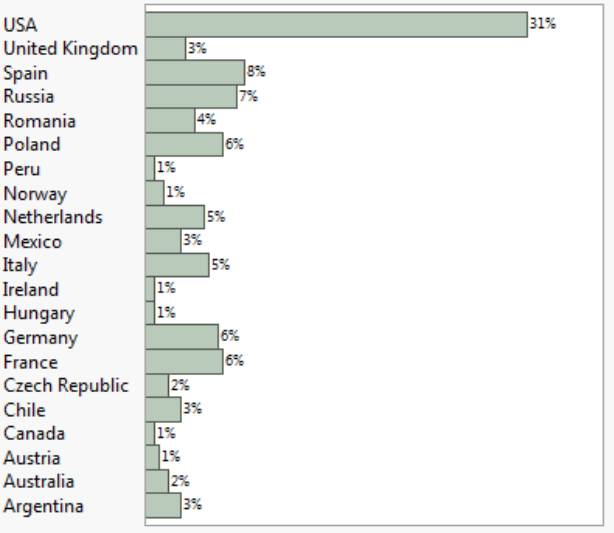


Figure 11: Study locations for the trial included many diverse countries (Source: CA209017 dataset; Reviewer Figure)

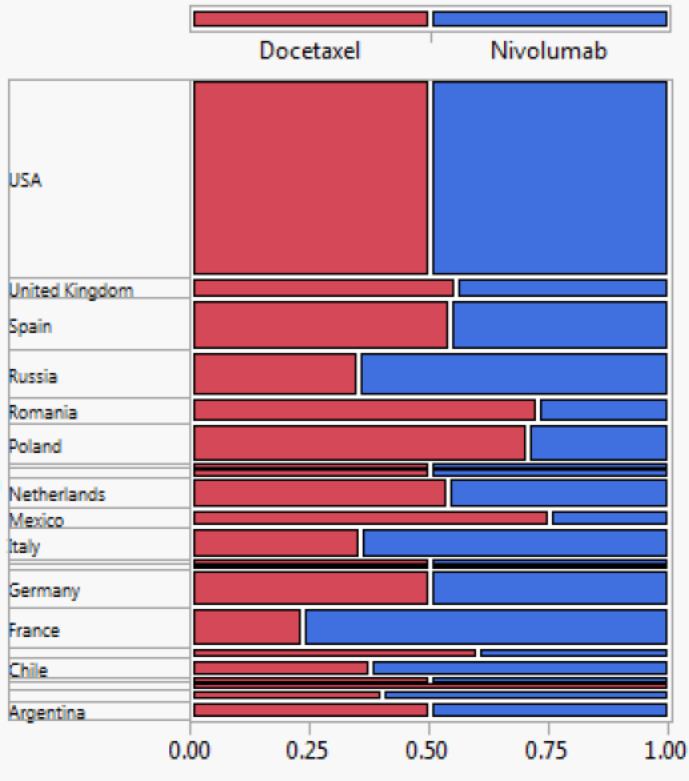


Figure 12: Distribution of patients in each arm by Study Location(Source: CA209017 dataset; Reviewer Figure)

Reviewer Note: The trial included many representative countries and a large population from the USA. As seen in Figure 11, certain countries enrolled more patients to a given arm.

Study stratification factors included geographical location (USA/Canada or Europe or rest of world) and Prior paclitaxel use (yes or no).

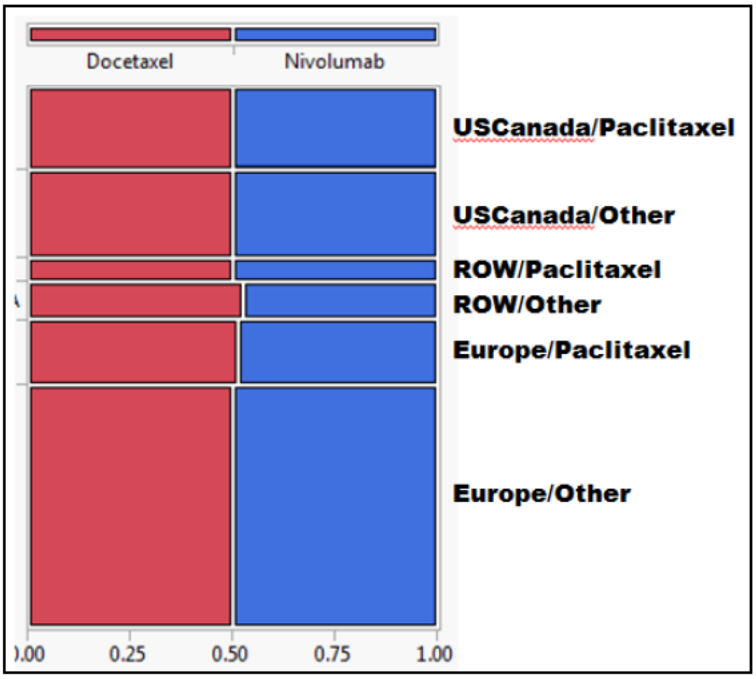


Figure 13: Balance of stratification factors between Arms **(Source: CA209017; Reviewer Figure)**

Reviewer Note: The stratification factors appeared well balanced between arms.

6.1.3_CA209017 Subject Disposition:

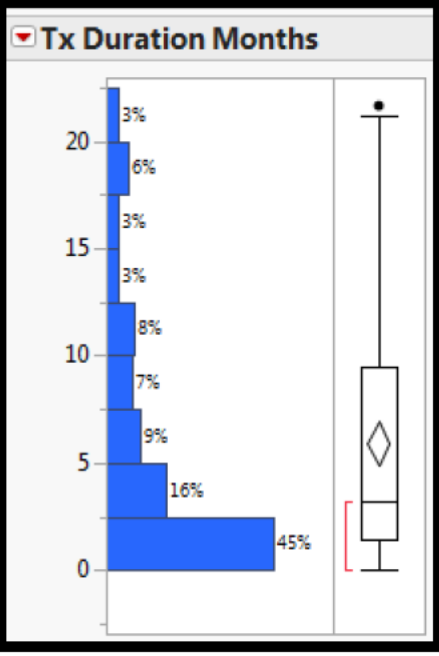
Enrollment of the study completed with 272 patients being randomly assigned to either receive nivolumab (n=135) or docetaxel (n=137). Of the 272 patients, 260 received at least one dose of either drug; 4 patients randomized to receive nivolumab and 8 patients randomized to receive docetaxel did not receive study drugs.

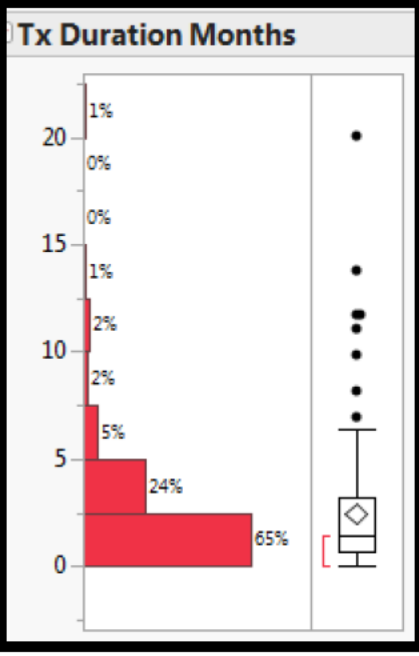
Table 11: Patient Disposition **(Source: CA209017 dataset; Reviewer Table)**

	Nivolumab	*Docetaxel*	*Total*
Intent to Treat (n)	135	137	272
Received ≥1 dose (n)	131	129	260
Continuing treatment	16%	1.6%	8.8%
Reason not continuing	84%	98%	91%
Disease Progression	67%	62%	65%
AE unrelated to drug	4.6%	10%	7.3%
Study drug toxicity	3.8	10%	6.9%
Maximum clinical benefit	1.5	5.4%	3.5%
Consent withdrawal	2.3	3.9%	3.1%
Request to discontinue	1.5	3.1%	2.3%
Excluded due to protocol	0.8%	1.6%	1.2%
Death	0.8%	0.8%	0.8%
Non-compliance	0.8%	0%	0.4%
Other	0.8%	1.6%	1.2%

Table 12: Duration of Treatment (Source: CA209017 dataset; Reviewer Table)

Duration of Treatment (Months)	Nivolumab	Docetaxel
Mean	5.9	2.5
Median	3.3	1.4
25% quartiles	1.4, 9.5	0.7, 3.2





6.1.4_CA209017 Analysis of Primary Endpoint: Overall Survival

Among the 272 randomized subjects, 199 subjects (73.2%) in total, 86 of whom received nivolumab and 113 of whom docetaxel, had a death event as of the data cutoff. Approximately 27% of the patients were still alive and therefore censored for the analysis. The O'Brien-Fleming boundary had a p-value of 0.0315 for the 199 deaths (86.1% of the 231 deaths required for the final analysis).

With patients undergoing a median follow-up of 16 months, nivolumab demonstrated a median OS benefit of 9.2 months compared to 6.0 months in the active control docetaxel arm (Figure 13, Table 12). This was a greater than 1.5-fold increase in median survival with a stratified hazard ratio of 0.59 (95% CI: 0.44, 0.79), p-value of 0.00025.

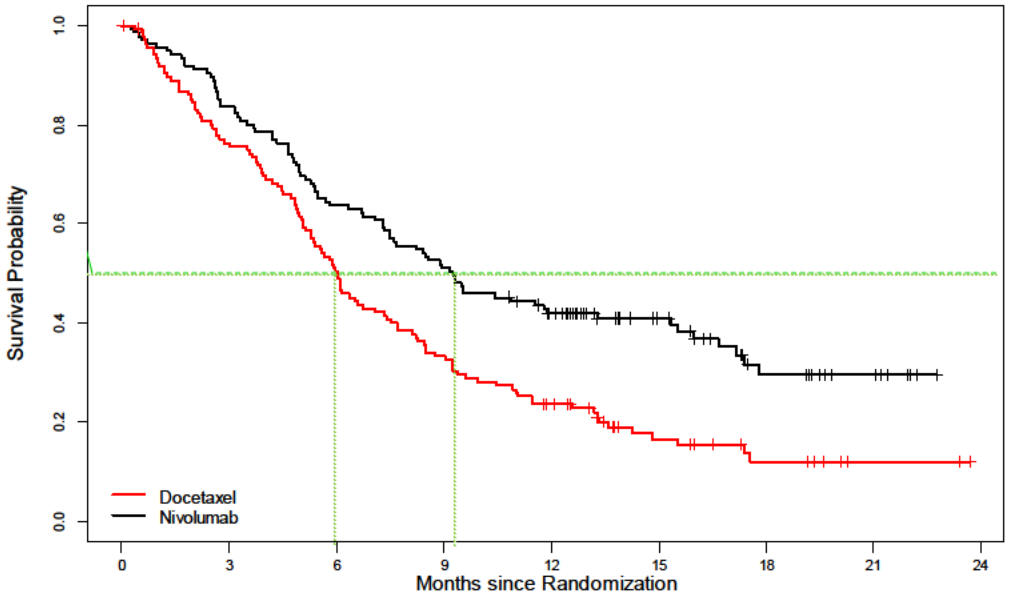


Figure 14: Kaplan-Meir Curves of Overall Survival (Source: CA209017 dataset; Reviewer Figure)

Table 13: Overall Survival Results for Study CA209017 (Source: CA209017 dataset; Reviewer Table)

Treatment Arm	Nivolumab (n=135)	Docetaxel (n=137)
Death, n (%)	86 (64)	113 (82)
Median (95% CI), months	9.2 (7.3, 13.3)	6.0 (5.1, 7.3)
Stratified HR (95% CI)*	0.59 (0.44, 0.79)	
Stratified p-value*	0.00025	

*The Cox proportional hazards model and log-rank test were stratified by prior paclitaxel use and region collected by IVRS

Reviewer Note: The nivolumab arm demonstrated a statistically significant and clinically meaningful 3.2 month improvement in median OS over docetaxel. Of note, the curves appear to continue to separate after the medians. This interim OS analysis was a very mature analysis with 199 deaths and 73 patients still alive.

6.1.5_CA209017 Analysis of Secondary Endpoints(s)

The secondary endpoints in this trial included progression free survival and objective response rate.

Reviewer Note: FDA based its decision to accept the submission based only on the OS results the DMC had analyzed. All the data including all efficacy and safety will be required for submission as post marketing requirement/commitments (PMC/PMR). This will involve an efficacy supplement where data will be submitted in CDISC format.

6.1.6_CA209017 Other Endpoints

The protocol also required either a formalin-fixed, paraffin-embedded tumor tissue block or unstained slides of tumor samples (archival or recent) for biomarker evaluation. An exploratory analysis was conducted evaluating the effect of PD-L1 positivity as defined by a 5% cutoff.

As the table below shows the number of subjects with quantifiable PD-L1 expression was slightly greater in the nivolumab arm than the docetaxel arm.

Table 14: Patients with quantifiable PD-L1 expression (Source: CA209017 dataset; Reviewer Table)

	Nivolumab ITT (n=135)	Docetaxel ITT (n=137)	Total ITT (n=272)
Patients with samples quantifiable for PD-L1 expression	**86.7%**	**78.8%**	**82.7%**
≥5% PD-L1 expression (positive)	**31.1%**	**28.5%**	**29.8%**
<5% PDL1 expression (negative)	**55.6%**	**50.4%**	**52.9%**

Table 15: Overall Survival based on PD-L1 positivity using a 5% cutoff (Source: CA209017 dataset; Reviewer Table)

	Nivolumab (n=135)	Docetaxel (n=137)
PD-L1 positive subgroup	42	39
Deaths, n (%)	26 (62)	33 (85)
Median (95% CI), months	10.0 (5.8, 17.1)	6.4 (4.5, 9.0)
HR (95% CI)	0.52 (0.31, 0.89)	
PD-L1 negative subgroup	75	69
Deaths, n (%)	50 (67)	55 (80)
Median (95% CI), months	8.5 (5.5, 13.3)	6.1 (5.1, 8.3)
HR (95% CI)	0.72 (0.49, 1.07)	
PD-L1 NQ subgroup	18	29
Deaths, n (%)	10 (56)	25 (86)
Median (95% CI), months	9.4 (7.1, NE)	5.1 (3.0, 6.1)
HR (95% CI)	0.62 (0.28, 1.40)	

NQ= Not Quantifiable; NE=Not Estimable
Note: HRs were estimated from Cox proportional hazards models stratified by prior paclitaxel use and region collected by IVRS

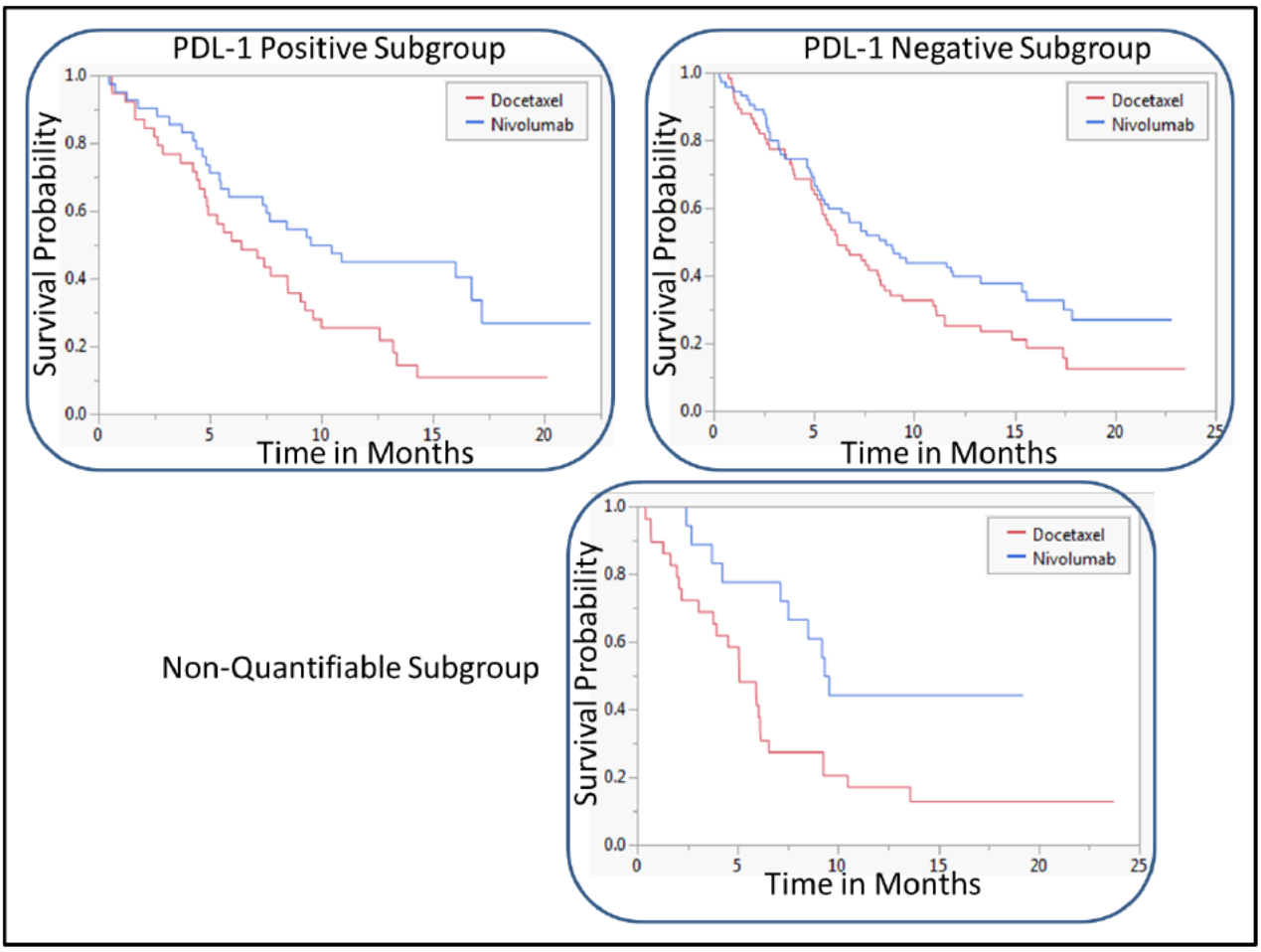


Figure 15: Kaplan Meir Curves of PD-L1 Subgroups (≥5% expression) **(Source: CA209017 dataset; Reviewer Figure)**

Reviewer Note: In a retrospective exploratory analysis, patients on the nivolumab arm had improved survival compared to the control arm irrespective of PD-L1 status, however PDL1 positivity may be predictive of improved outcomes.

6.1.7_CA209017 Subpopulations

The table below represents subgroup analysis regarding gender, race, nationality, performance status, prior paclitaxel use, and age.

Table 16:Subgroup analysis of overall survival by baseline factors (Source: CA209017 dataset; Reviewer Table)

	Nivolumab (n=135)		Docetaxel (n=137)		
	#events/Total N(%)	Median (months)	#events/Total N(%)	Median (months)	HR (95% CI)*
Overall	86/135 (64)	9.2	113/137 (82)	6.0	0.59 (0.45, 0.78)
Gender					
Male	71/111 (64)	9.3	82/97 (85)	5.7	0.57 (0.41, 0.78)
Female	15/24 (62)	7.3	31/40 (77)	7.5	0.67 (0.36, 1.25)
Race					
White	79/122 (65)	9.2	109/130 (84)	6.0	0.59 (0.44, 0.79)
Others	7/13 (54)	9.3	4/7 (57)	5.8	0.72 (0.21, 2.50)
Region					
U.S.	28/42 (67)	9.1	33/42 (79)	5.6	0.62 (0.38, 1.03)
Non-U.S.	58/93 (62)	9.3	80/95 (84)	6.1	0.58 (0.41, 0.82)
Region					
Europe	47/77 (61)	9.5	69/78 (88)	6.0	0.50 (0.34, 0.72)
US/Canada	28/43 (65)	9.2	34/43 (79)	5.3	0.59 (0.36, 0.98)
Rest of the world	11/15 (73)	9.2	10/16 (62)	6.3	1.54 (0.65, 3.64)
Prior Paclitaxel Use (IVRS)					
Yes	26/43 (60)	9.2	36/44 (82)	5.0	0.51 (0.31, 0.84)
No	60/92 (65)	9.2	77/93 (83)	6.1	0.64 (0.45, 0.89)
Age					
<65	48/79 (61)	9.5	61/73 (84)	6.1	0.52 (0.35, 0.76)
>=65	38/56 (68)	7.6	52/64 (81)	5.9	0.70 (0.46, 1.06)
ECOG PS					
0	11/27 (41)	NR	24/37 (65)	10.7	0.49 (0.24, 0.99)
1	73/106 (69)	8.0	89/100 (89)	5.3	0.54 (0.39, 0.74)

* estimated from unstratified Cox proportional hazards models

Reviewer Note: Exploratory subgroup analysis of survival based on baseline variables favor the nivolumab arm with the exception of “rest of world”, a small subgroup with wide confidence intervals.

STUDY CA209063

Table 17: Data cutoff dates for submissions

Data Submission	*Data Type*	*Report Date*	*Database Lock Date*
sBLA	CSR and Data Sets	11/5/2014	8/15/2014
Addendum	CSR and Data Sets	7/16/2014	3/19/2014
Safety Update	120-Day Safety	1/30/2015	
	Study Start Date: 11/16/2012 Study End Date: 6/11/2014		

Reviewer Note: This review is primarily based on the data provided in the addendum (most up to date), unless otherwise noted.

6.1.2_CA209063 Demographics

Table 18: Study demographics and disease characteristics for study CA209063
(Source: CA209063 CSR; Reviewer Table)

Study Characteristics		Nivolumab (n=117)
Age	Median ≥65 ≥75	64 50% 14%
Sex	Male	73%
Race	White Black	85% 9%
Histology	Squamous	100%
Stage	IIIb IV	6% 94%
ECOG PS	0 1	22% 78%
Number of Prior Treatments Received	Median	3
CNS Metastasis	Yes	1.7%

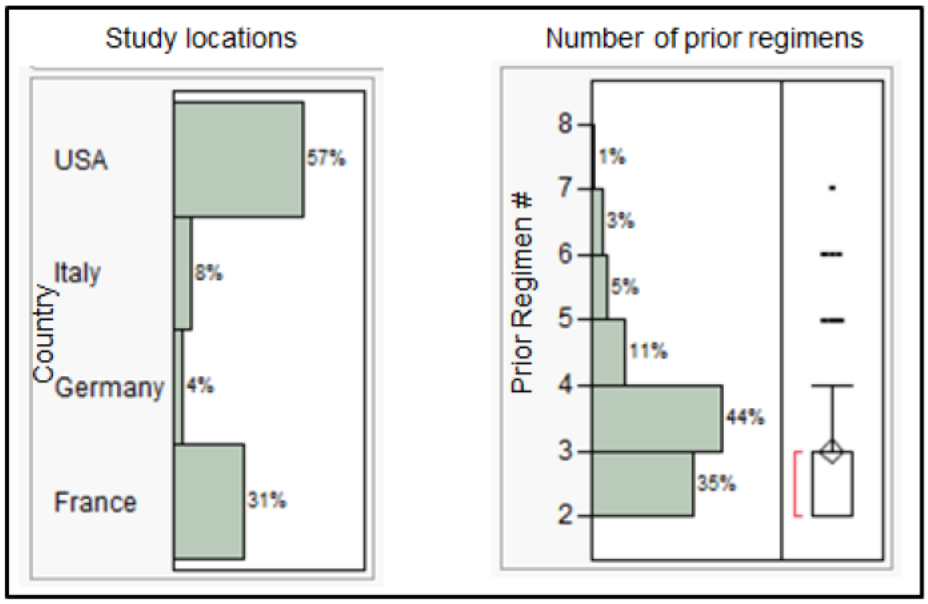


Figure 16: Representation of enrollment by country and number of prior regimens
(Source: CA209063 CSR; Reviewer Figure)

Reviewer Note: All patients on this study had NSCLC with squamous histology. The study did enroll a large number of males and the majority of patients enrolled were from the USA. Most patients had at least 3 prior lines of therapy (44%) followed by 2 prior lines (35%).

6.1.3_CA209063 Subject Disposition

Table 19: Subject Disposition (Source: CA209063 CSR; Reviewer Table)

Category	Subcategory of Event	Disposition Event	Nivolumab 3 mg/kg	
			N	%
Screening	Number of Patients Screened		140	
	Number of Patients Enrolled		117	
	Number of Patients Not Enrolled	No Longer Meet Eligibility	20	
		Death	2	
		Lost to Follow Up	1	
Protocol Milestone		Informed Consent Obtained	117	100.0
		Pgx Informed Consent Obtained	93	79.5
Disposition Event	Death Status	Death	72	61.5
	Study Discontinuation	Not Continued	75	64.1
		Continued	42	35.9
	Treatment Discontinuation	Disease Progression	78	66.7
		Study Drug Toxicity	14	12.0
		Adverse Event Unrelated To Study Drug	9	7.7
		Subject Requested To Discontinue	1	0.9

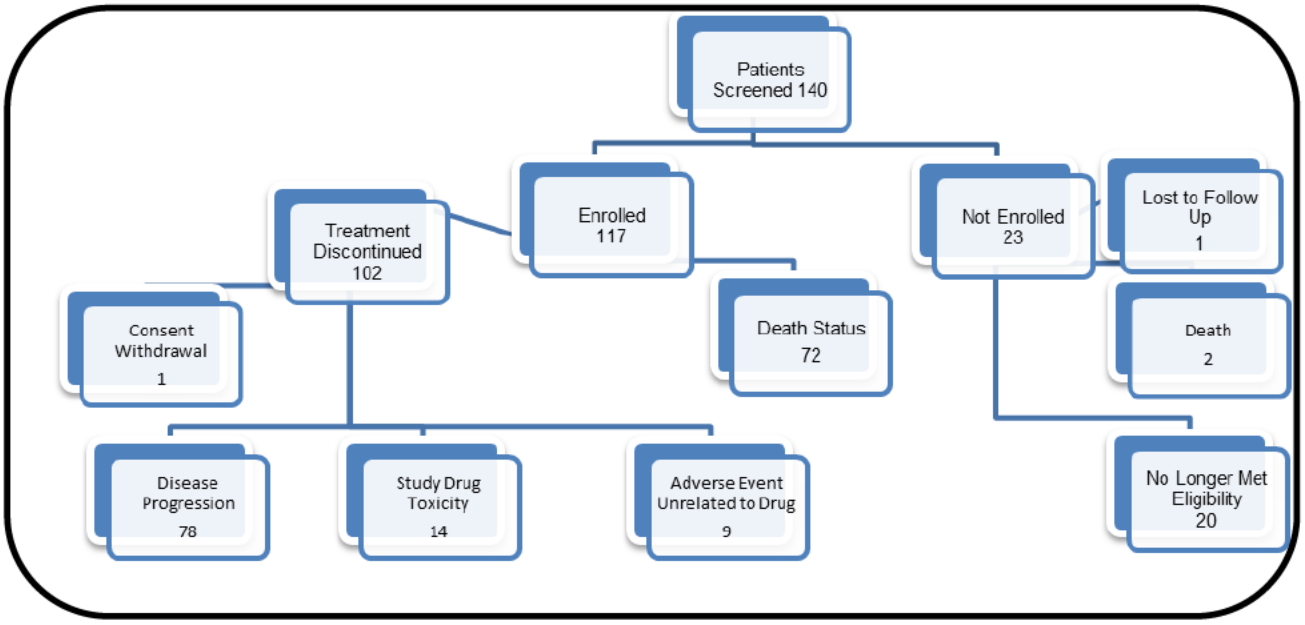


Figure 17: Disposition of patients on Study CA209063 **(Source: CA209063 CSR; Reviewer Figure)**

Reviewer Note: No significant concerns were observed regarding patient disposition.

Treatment Exposure:

Table 20: Patient exposure to treatment **(Source: CA209063 CSR; Reviewer Table)**

Nivolumab	*Duration of Treatment (Months)*	*Doses received (number)*
Mean	4.1	9.3
Median	2.3	6.0
25% quartiles	0.9, 6.3	Range: 1-34

6.1.4_CA209063 Analysis of Primary Endpoint

The primary endpoint for this study was IRC-derived ORR.

Table 21: Primary endpoint of ORR by IRC for study CA209063 (Source: CA209063 CSR; Reviewer Table)

	ORR	95%CI (exact)	DoR	95%CI
IRC	14.5%	8.7, 22.2	Not Reached	8.3, NR

13 of the 17 patients (76%) with confirmed responses had ongoing responses ranging from 1.9+ to 11.5+ months. 10 of these 17 patients (59%) had durable responses of 6 months or longer.

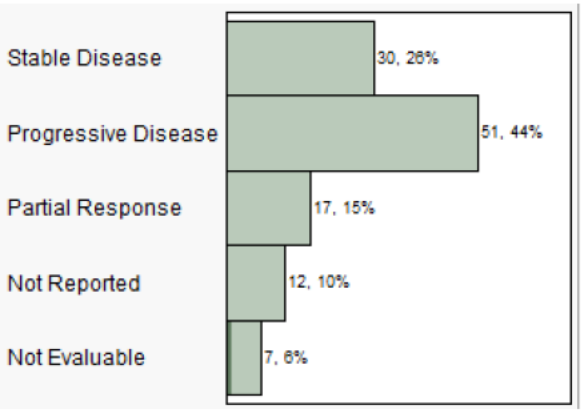


Figure 18: Responses observed by the IRC (Source: CA209063 CSR; Reviewer Figure)

Reviewer Note: Reasons that the IRC indicated that responses were not evaluable included:

- Patients underwent radiotherapy prior to first study scan
- Second follow-up scan was too early or incomplete

Reasons that, due to a lack of on-study scans, responses were not reported:

- Death prior to assessment
- Early discontinuation due to toxicity
- Investigator assessment of progressive disease
- Clinical progression without scans
- Patient withdrawal
- Study discontinuation prior to scans

6.1.5_CA209063 Analysis of Secondary Endpoints(s)

The Secondary endpoint of this study was investigator-derived ORR.

Table 22: Secondary endpoint of ORR by investigator for study CA209063 (Source: CA209063 CSR; Reviewer Table)

	ORR	95%CI
Investigator	14.5%	8.7, 22.2

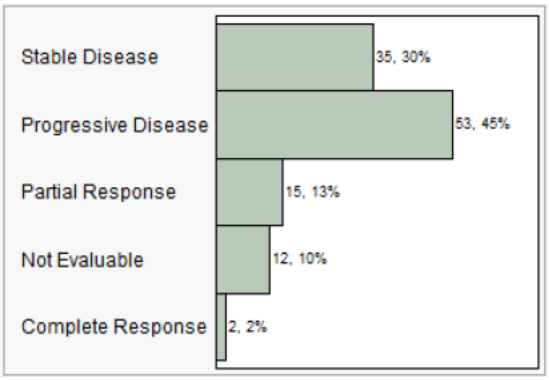


Figure 19: Responses observed by the investigator (Source: CA209063 CSR; Reviewer Figure)

Reviewer Note: ORR results were consistent per IRC and investigator assessments.

6.1.6_CA209063 Other Endpoints

Exploratory endpoints included determination of PFS, OS, and PD-L1 biomarker assessment.

Table 23: Secondary endpoint of OS for study CA209063 (Source: CA209063 CSR; Reviewer Table)

Overall Survival	
Median OS	8.2 months
6-month OS	60.1%
1-year OS	40.8%
Patients with death event at time of analysis	72/117 (62%)
Death events due to disease	63/72 (88%)
Death events due to toxicity	2/72 (3%)

Table 24: Exploratory endpoint of PFS by IRC for study CA209063 (Source: CA209063 CSR; Reviewer Table)

PFS IRC	
Median PFS	1.9 months
6-month PFS	25.9%
1-year PFS	20.0%

In this study, PD-L1 expression was an exploratory endpoint. Of the 117 patients who received treatment, 76 had samples which were evaluable for this biomarker. The table below displays exploratory retrospective efficacy endpoints based on three different cut-off points for PD-L1 positivity.

Table 25: Number of patients with PD-L1 positivity based on cutoffs and ORR (IRC) and mOS in the respective subgroups (Source: CA209063 CSR; Reviewer Table)

		<1%	<5%	<10%
Patients (N)	Negative Positive	31 45	51 25	51 25
ORR	Negative % Positive %	12.9 (3.6,29.8) 20.0(9.6,34.6)	13.7 (5.7,26.3) 24.0 (9.4,45.1)	13.7 (5.7,26.3) 24.0 (9.4,45.1)
mOS		8.3 vs 10.1	8.2 vs 15.7	8.2 vs 15.7

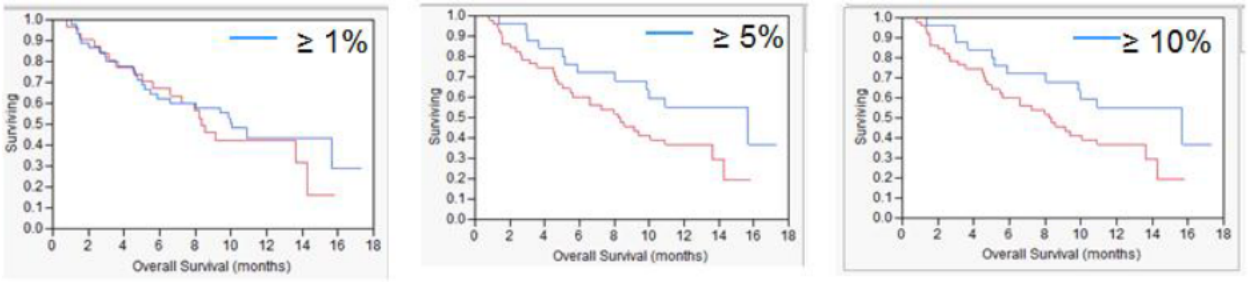


Figure 20: Kaplan Meir curves for OS based on cut-off used for PD-L1-positivity (Source: CA209063 CSR; Reviewer Figure)

Reviewer Note: In a retrospective exploratory analysis of ORR and OS, nivolumab appeared to have activity irrespective of PD-L1 expression. However, it does appear that PD-L1 "positive" patients have a greater likelihood of response. In this study, there was no apparent difference between 5% and 10% cut-off points for PD-L1-positivity.

Study CA20963 allowed for investigators to treat beyond RECIST v1.1-progression, if the following criteria were met:

- The investigator-assessed clinical benefit
- Treatment beyond progression did not delay an imminent intervention to prevent serious complications of PD
- The subject did not have rapid PD
- The subject tolerated the study drug, had stable performance status, and provided written informed consent prior to receiving additional nivolumab treatment

In this study, 20 patients (17%) were treated beyond progression and the spider plot below shows their change in target lesion tumor burden.

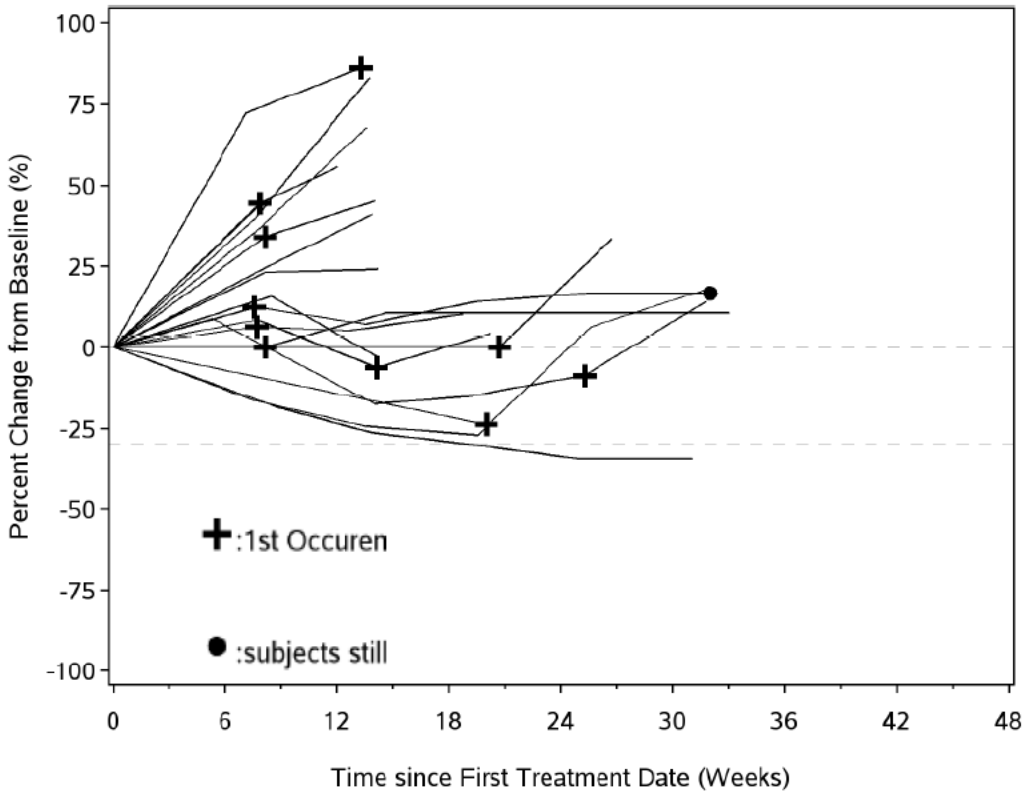


Figure 21: Spider plot of patient who were treated beyond progression (Source: CA209063 CSR; Sponsor Figure)

Of these 20 patients, 4 (3%) were considered to have non-conventional benefit as defined by the sponsor.

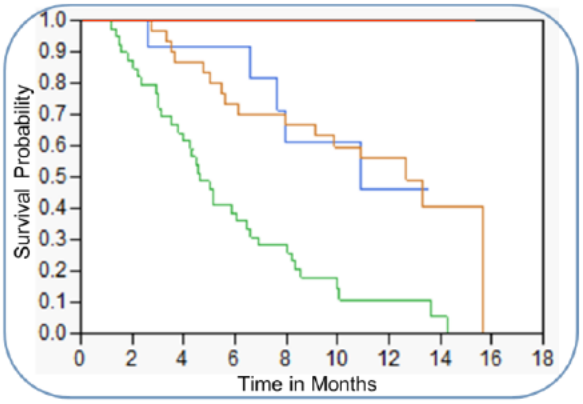
- One patient had a response in target lesions but appearance of a new lesion.
- Three patients had progression but no further progression (10% additional increase) for at least 2 tumor measurements.

Table 26: Patients who experience sponsor-defined non-conventional benefit (BoR=best overall response; BL=baseline; DoT=duration of treatment; NT=non-target lesion; NL=new lesion) (Source: CA209063 CSR; Reviewer Table)

Patient	Inv BoR	# of Prior Regimens	Pre PD %Δ BL	Post PD %Δ BL	Reason for PD	# of Doses beyond PD	DoT beyond PD	Survival
63084	PD	2	↓ 18.7%	↓ 34.6%	PD NT	6	4.7	8.2+
63068	SD	2	0	↑ 10.5%	PD NT	6	2.9	7.6+
63097	PD	3	n/a	↓23.7%	NL	6	2.5	6.6
63112	PD	2	↑ 12.3%	↑ 16.7%	PD NT; NL	13	5.7+	7.5+

Reviewer Note: Based on the provided treatment beyond progression information, a few patients (<5%) may ultimately benefit despite initial progression. However, it is not clear who these patients are, and more information and studies will need to be conducted to describe and characterize this benefit.

FDA performed a responder analysis for survival to evaluate any association between survival and best overall response.



Best Overall Response per IRC	K-M color	% of patients	mOS Months
Objective Response		17 (15%)	No Events
Stable Disease		39 (33%)	12.7 mo
BoR =PD but treated beyond PD		12 (10%)	10.9 mo
Progressive Disease		30 (26%)	4.6 mo

Figure 22: Responder analysis: OS based on initial RESIST best overall response (Source: CA209063 CSR; Reviewer Figure)

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Reviewer Note: In this retrospective exploratory analysis, survival is associated with response. Interestingly, all patients who had a RESIST response remained alive at the time of database lock.

The primary endpoint of IRC-determined ORR was evaluated in subgroups

Table 27: ORR in subgroups (Source: CA209063 CSR; Reviewer Table)

Subgroup	*IRC-ORR %*
ITT population	15
Male	19
Female	3
Age <65	12
Age ≥65	17
Race Black	18
Race White	15
Prior Lines of Therapy:	
2	10
3	17
≥4	17

Reviewer Note: Nivolumab appeared to have activity in different subpopulations. In this study, the ORR was lower in the female population; however, given the subgroup analysis results from Study CA209017, lack of activity in females is not a concern.

6.1.8_CA209063 Analysis of Clinical Information Relevant to Dosing Recommendations

Please see Clinical Pharmacology Review

6.1.9_CA209063 Discussion of Persistence of Efficacy and/or Tolerance

Not relevant.

6.1.10_CA209063 Additional Efficacy Issues/Analyses

An information request was sent to BMS to clarify why some patients who were listed as having Stage IIIB disease had metastatic sites listed as target lesions. Based on BMS's analysis, of the 20 patients who were listed as having IIIb disease on their CRFs at least 13 had recurrent/metastatic Stage IV disease. Therefore at least 94% of patients had metastatic disease. However, based on subgroup analyses, there was no difference in efficacy between recurrent IIIb and IV patients.

7 Review of Safety

Safety Summary

The primary analysis of safety was based on Study CA209063, a single arm trial of nivolumab at the recommended dose of 3 mg/kg (N=117) in patients with advanced SQ NSCLC whose disease has progressed during or after both platinum doublet-based chemotherapy and at least 1 additional systemic therapy. Supportive safety data was provided by Study MDX1106-03 in multiple tumor types including patients with refractory SQ NSCLC treated at the recommended dose of nivolumab or higher (3 or 10 mg/kg Q2W). The data provided by the applicant allowed satisfactory characterization of nivolumab's safety profile in patients with advanced SQ NSCLC.

In Study CA209063, the median duration of therapy was 2.3 months (1 to 16.1). Patients received a median of 6 doses of treatment (1 to 34). The trial excluded patients

with active autoimmune disease, symptomatic interstitial lung disease, or untreated brain metastasis. The median age of patients was 65 years. The majority of patients were male (73%) and white (85%). Baseline disease characteristics of the population were recurrent Stage IIIB (6%), Stage IV (94%), and brain metastases (1.7%). Baseline ECOG performance status was 0 (22%) or 1 (78%).

Treatment discontinuation and treatment delays due to adverse reactions occurred in approximately one third of patients in each category. Grade 3-4 and serious adverse reactions occurred in approximately 60% of patients in each category and included dyspnea, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, hemoptysis, and pain. Grade 3-4 laboratory abnormalities occurring in greater than 2% of patients included hyperkalemia, hypercalcemia and anemia.

Common adverse reactions of any Grade occurring in greater than 30% of patients included fatigue, dyspnea, decreased appetite and cough. Common laboratory abnormalities of any Grade occurring in greater than 20% of patients included lymphopenia, hyponatremia, and anemia. Immune-mediated adverse reactions included pneumonitis (7 patients), hypothyroidism (5 patients), hyperthyroidism (2 patients), colitis, and renal dysfunction (one patient each). Immune-mediated adverse reactions were generally manageable with supportive care measures including corticosteroids and/or dose interruptions/discontinuations. The safety findings in Study MDX1106-03 were generally consistent with the finding in Study CA209063. A notable exception was occurrence of 5 fatal cases of pneumonitis in Study MDX1106-03, possibly related to suboptimal medical management including delay in administration of corticosteroids.

Based on the data provided by the applicant and in the context of the large unmet medical need of the disease being treated, the safety profile of nivolumab in patients with advanced SQ NSCLC is acceptable. Further characterization of the safety profile of nivolumab will be achieved by analyzing randomized trial data as described in section 1.4.

7.1 Methods

The primary analysis of safety for nivolumab for the proposed indication was based on Study CA209063 in previously treated patients with advanced squamous NSCLC with supportive safety data from study MDX1106-03 in multiple tumor types, including NSCLC. Unless otherwise stated, the primary safety analyses are based on updated July 8, 2014 database lock, which amended the final CSR with a clinical database lock of March 6, 2014.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Study CA209063 (primary safety): "Phase 2" single arm trial of nivolumab 3 mg/kg monotherapy (N = 117) in patients with advanced squamous (SQ) NSCLC whose disease has progressed during or after both platinum doublet-based chemotherapy and at least 1 additional systemic therapy. Patient demographics are shown in Table 28.

Table 28. Patient demographics in Study CA209063

Characteristics		**N=117**	
Age	Mean	64.1	
	Min	37	
	Q1	57	
	Median	65	
	Q3	71	
	Max	87	
		Count	**%**
Age Group	Age under 65 years	58	49.6
	65 <= Age <75	43	36.8
	Age 75 and over	16	13.7
Sex	Female	32	27.4
	Male	85	72.6
Race	Asian	2	1.7
	Black Or African American	11	9.4
	White	99	84.6
	Other	5	4.3
Ethnicity	Not Hispanic Or Latino	69	59.0
	Not Reported	48	41.0

Study MDX1106-03 [CA209003] (supportive safety; n=306; database lock of February 4, 2013): This study was a "Phase 1," open-label, multicenter, multi-dose, dose-escalation study of nivolumab. Each treatment cycle was comprised of 4 doses of study drug administered on Days 1, 15, 29, and 43, with a tumor response assessment between Days 52 and 56. The response assessment was completed before the first dose in the next cycle of treatment. Subjects, who progressed during the follow-up phase and were eligible, were allowed to be re-treated for up to another 96 weeks. Following completion and/or discontinuation of the treatment and follow-up periods, all subjects were followed for survival.

Dose escalation in Study MDX1106-03 proceeded at 1, 3, and then 10 mg/kg. Three subjects at a time were enrolled at the 1 and 3 mg/kg dose levels whereas 6 subjects were enrolled at one time at the 10 mg/kg dose level. One DLT was reported in 1 of the 6 subjects treated with 10 mg/kg nivolumab during the dose escalation phase. Subject MDX1106-03-1-3301 in the 10 mg/kg treatment group developed Grade 3

myelodysplastic syndrome (MDS) considered related to study drug. Since the DLT rate was no more than 1/6 subjects, the trial was allowed to enter the expansion phase. No further cases of MDS were reported in MDX1106-03. Fourteen expansion cohorts were enrolled. Subjects in Study MDX1106-03 had mCRPC, RCC, CRC, melanoma, or NSCLC, confirmed by available pathology records or biopsy, that was advanced (non-resectable), or recurrent and progressing since last antitumor therapy, and for which no alternative, curative standard therapy existed. The safety population included following subjects:

1) Advanced SQ NSCLC treated with 3 mg/kg (n=18)

2) All other tumor types treated with 3 mg/kg (n=36)
    a. Non-squamous (NSQ) NSCLC (n=19)
    b. Melanoma (n=17)

3) All tumor types treated with 10 mg/kg (n=131)
    a. SQ NSCLC
    b. NSQ NSCLC
    c. Renal cell carcinoma
    d. Melanoma
    e. Metastatic castrate resistant prostate cancer
    f. Colorectal cancer

7.1.2 Categorization of Adverse Events

Study CA209063: Safety and tolerability assessment was based on frequency of deaths, adverse events (AEs), serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose delay, select AEs, clinical laboratory assessments (hematology, serum chemistry, and liver and thyroid function tests), and vital sign measurements. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. The MedDRA preferred terms (PT) and the corresponding verbatim terms included in the datasets were reviewed to check for accuracy of MedDRA coding using both random audit and automated character analysis conducted by FDA Jump Start service. Comparison of the applicant's MedDRA PTs to the verbatim terms did not show significant discrepancies. Adverse events and laboratory values were graded for severity using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Study MDX1106-03: AEs were coded using the MedDRA Version 15.1, and graded for severity using NCI CTCAE Version 3.0. AEs, SAEs, select AEs, and AEs leading to discontinuation were tabulated by treatment and across treatments for each tumor type and across tumor types.

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

N/A

7.2 Adequacy of Safety Assessments

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

In Study CA209063, the median number of nivolumab doses received was 6 (1 to 34) and the median duration of therapy was 2.33 months (1 to 16.1). All 117 subjects received at least 1 dose of nivolumab. The demographics of the safety population were similar to the efficacy population.

In Study MDX1106-03, the median duration of therapy across all tumor types was 3.7 months. In the 21 subjects treated with nivolumab at 3mg/kg, the median duration of exposure was 6.2 months (1 to 24). Similar to CA209063, the majority of subjects had Stage IV disease and all had received at least 1 prior therapy. Most subjects were male (57.1%) nearly all subjects were white (95.2%). The median age was 67 years (53 to 83).

Overall, the size of the safety population and the extent of exposure in the 2 trials were adequate and generally allowed sufficient characterization of AEs associated with nivolumab in the target patient population.

7.2.2 Explorations for Dose Response

The primary analysis of safety was conducted in patients receiving the recommended dose and schedule.

7.2.3 Special Animal and/or In Vitro Testing

N/A.

7.2.4 Routine Clinical Testing

In Study CA209063, the following assessments were planned starting on Cycle 1 Day 1 and continued at regular intervals and as needed:

- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also amount of supplemental oxygen if applicable) within 72 hours of dosing.
- AEs continuously throughout the study.

- Physical examination and physical measurements including weight, and ECOG performance status.
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results were to be obtained prior to dosing on infusion days).
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose and LDH), (results were to be obtained prior to dosing on infusion days).
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results were to be obtained prior to dosing on infusion days).
- Thyroid function testing including TSH (reflex to free T3 and free T4 if abnormal result).
- Pregnancy test performed every 6 weeks on study or more frequently as per local standards.

The routine clinical testing in Study CA209063 appears to have been generally sufficient to elicit adequate adverse event data.

7.2.5 Metabolic, Clearance, and Interaction Workup

See original BLA review.

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

To support the primary analysis of safety, the applicant made reasonable efforts to characterize select AEs that may be common across immune checkpoint inhibitors. These select AEs included the following domains:

- Endocrine
- Gastrointestinal
- Hepatic
- Pulmonary
- Renal
- Skin
- Hypersensitivity/infusion reactions

7.3 Major Safety Results

7.3.1 Deaths

The summary of all deaths in Study CA209063 are shown in Table 29.

Table 29. Summary of deaths in Study CA209063, all treated population

Total Number of deaths		**72**
Reported causes of death		
DISEASE	N	63
	% of Total	87.50
OTHER	N	7
	% of Total	9.72
STUDY DRUG TOXICITY	N	2
	% of Total	2.78
Reasons for deaths reported as "OTHER" and "STUDY DRUG TOXICITY"		**Days from death to last dose**
MENINGITIS		75
HYPOXIC PNEUMONIA*		29
INTRACRANIAL HEMORRHAGE		76
ISHEMIC STROKE*		41
MORPHINE DRUG INTOXICATION		3
PNEUMONIA, RESPIRATORY FAILURE		16
RUPTURED AORTIC ANEURYSM		13
SEPTIC SHOCK (2 cases)		9
		100

*These 2 cases were reported as "STUDY DRUG TOXICITY."
Refer to case narratives below for more information on these subjects.
Reviewer analysis, ADSL dataset

The median number of days in Study CA209063 from death to last dose was 99 (3, 391) and 29 (3, 100) for disease related and not disease related deaths, respectively [reviewer analysis]. A total of 14 of 72 deaths (19.4%) occurred from the first dose up to 30 days after last dose, 9 of which were likely disease related [reviewer analysis]. Deaths possibly not related to disease progression are summarized in Table 30.

Table 30. Summary of patient narratives with deaths assessed as not related to disease progression (i.e., "OTHER" or "STUDY DRUG TOXICITY) in Study CA209063

Patient ID: CA209063-12-63070
HAEMORRHAGE INTRACRANIAL (GRADE 5, REPORTED NOT DRUG RELATED, DAY 120)
68-year old female with stage IV SQ NSCLC and metastases in the lung, lymph nodes and peritoneum. On day 57, a computed tomography (CT) scan revealed disease progression. The study therapy was discontinued on Day 60 due to disease progression with the last dose received on day 46. On day 120, 74 days post the 4th (last) dose of study therapy; CT scan of the head showed massive acute subarachnoid hemorrhage and left facial fractures. Repeat CT scan of the head on the same day (day 120), showed significant progression of disease, extensive subarachnoid hemorrhage shown to be secondary to aneurysm and a new right subdural hemorrhage. An electrocardiogram showed non-specific ST/T wave changes and blood chemistry results were not clinically significant per the Investigator (although specific laboratory test results were not provided). The investigator reported a serious adverse event of intracranial hemorrhage, considered to be not related to the study therapy. The subject was placed on comfort care, as review of images suggested that the subject had a bleeding aneurysm that the

neurosurgical team considered was beyond intervention. The cause of death reported as intracranial hemorrhage. It is not known whether an autopsy was performed.
Reviewer comments: The information provided supports death in the context of intracranial hemorrhage which may not have been related to study drug.
Patient ID: CA209063-13-63097
MENINGITIS (GRADE 5, REPORTED NOT DRUG RELATED, DAY 192)
61-year old female with stage IIIB squamous non-small cell lung carcinoma and metastases to the lung and lymph nodes. The subject's relevant medical history included non-insulin dependent diabetes mellitus. Subject was discontinued from study therapy on day 141 due to disease progression. She received the last dose of study therapy on day 127. Subject was started on standard care regimen of weekly gemcitabine on day 169. On day 192, 65 days post the 10th (last) dose of nivolumab, the subject was hospitalized with weakness, vomiting, acute respiratory distress, left gaze preference, decreased alertness, and diplopia, all symptoms of a clinical diagnosis of seizure. A CT scan of the head on day 191, showed "negative findings." The subject was intubated for ventilator support and began treatment with levetiracetam 500 mg every 12 hours. On day 193, a magnetic resonance imaging scan of the brain showed extensive meningitis, ependymitis, and ventriculitis with frank pus layering in the ventricles and superimposed acute hydrocephalus and perventricular edema. Chest x-ray results were normal and urine culture was positive for microorganism. Cerebrospinal fluid (CSF) on day 193 was negative for malignancy but CSF culture was positive for Streptococcus anginosus. The Investigator reported a serious adverse event of meningitis considered not related to study therapy, with onset of day 192. The subject was treated with vancomycin, ampicillin, ceftriaxone, ceftazidime and cefepime. On day 197, a respiratory culture and quantitative mini-bronchoalveolar lavage was positive for gram positive cocci. On day 201, the subject died. It is not known whether an autopsy was performed.
Reviewer comments: The information provided supports the assessment that death was in the context of meningitis, with positive CSF culture for Streptococcus anginosus, which may not have been drug related.
Patient ID: CA209063-14-63022
MORPHINE DRUG INTOXICATION (GRADE 5, REPORTED AS DRUG NOT RELATED, DAY 31)
75-year old male with stage IV squamous non-small cell lung carcinoma. On day 31, 2 days post the 3rd dose of nivolumab infusion, subject suddenly died and the cause of death was reported to be due to toxicity to various agents (morphine drug intoxication). His concomitant medications included acetaminophen 325 mg/hydrocodone 5 mg, aspirin 81 mg, bupropion 150 mg, calcium/vitamin D, citalopram 40 mg, zolpidem 10 mg, enoxaparin 120 mg, gabapentin 400 mg, morphine 30 mg (extended release 30 mg tablet, every 12 hours), multivitamins with iron and minerals, and cyanocobalamin. An autopsy was performed and the toxicology of liver showed morphine sulphate of 4 mg/kg (lethal). He received the last dose of study therapy on day 29 ((b) (6)). The investigator considered the event of toxicity to various agents to be not related to the study therapy.
Insufficient information to fully assess cause of death, although the autopsy result supports death in the setting of morphine use.
Patient ID: CA209063-14-63035
HYPOXIC PNEUMONIA (GRADE 5, REPORTED AS DRUG RELATED, DAY 65)
45-year old male with squamous non-small cell lung carcinoma and metastases in bone, mediastinum and pleura. Subject's relevant medical history included hemopneumothorax and prior thoracic radiotherapy. On day 56, 13 days after his 4th dose of nivolumab, CT scan showed unequivocal disease progression in bone and pleural lesions. The study therapy was discontinued due to disease progression, with the last dose received on day 43. On day 65, 22 days post the last dose of nivolumab, the subject presented to the hospital with a 3 day history of pyrexia (temperature of 37-38° Celsius [C]) and dyspnea and admitted with a diagnosis of pneumonia reported as "hypoxic pneumonia." Treatment with ceftriaxone, levofloxacin, albuterol and oxygen (O2) therapy was initiated. CT scan on day 67 showed an interstitial pattern predominant in the posterior segments of the upper right and lower right lobes and no pleural effusion. On day 68, an initial dose of intravenous methylprednisolone 230 mg was administered. A bronchoscopy and bronchoalveolar lavage was not performed due to his clinical status. The subject's

hypoxia increased and on day 71 as he experienced acute respiratory failure and died.
Please see section following this table for more information about this patient.
Patient ID: CA209063-20-63107
SEPTIC SHOCK (GRADE 5, REPORTED AS NOT DRUG RELATED, DAY 31)
75-year old female with stage IV squamous non-small cell lung carcinoma and renal, lymph node and pericardium metastases, including pericardial effusion and right pleural effusion. The subject's relevant medical history included palpitation lower limb edema, and dyspnea. On day 36, she experienced acute respiratory distress associated with hyperthermia and coma (Glasgow score 3/15). She was transferred to intensive care unit for further management. Blood culture was positive for K. oxytoca and E. coli. The subject received supportive therapy and cefotaxime. On the same day (day 36), an abdominal ultrasound showed intra-caval thrombus and ascitic effusion. She was noted with acute renal failure that concluded in multi-organ failure most likely secondary to septic shock. A serious adverse event of septic shock with onset date of day 31 was reported, which the Investigator considered not related to study therapy. On day 37 the subject died, with cause of death reported as septic shock. An autopsy was not performed. The last dose of study therapy was received on day 29.
Reviewer comment: The information provided, including the clinical history and positive blood cultures, support death in the setting of multiorgan failure, which may have been due to septic shock.
Patient ID: CA209063-22-63081
PNEUMONIA (GRADE 5, REPORTED AS NOT DRUG RELATED, DAY 89)
58-year old male with stage IV squamous non-small cell lung carcinoma. The subject's relevant medical history included hypertension, hyperlipidemia, diabetes, and former tobacco use. On day -7, prior to initiation of study therapy, adverse events of Grade 2 asthenia and Grade 1 dyspnea were reported. Both the events were considered by the Investigator to be not related to the study therapy. On day 32, 4 days post the 3rd dose of nivolumab, the subject was hospitalized with a fever a serious adverse event of Grade 3 pneumonia (recorded as verbatim term post obstructive pneumonia), that was considered by the Investigator to be not related to study therapy. On day 34 a CT scan of the chest showed complete right upper lobe consolidation and atelectasis, considered presumably post obstructive. The subject was treated with vancomycin, piperacillin-tazobactam, albuterol/ipratropium, levofloxacin, and amoxicillin/clavulanic acid. The study therapy was delayed due to the event of pneumonia. On day 42, the event of pneumonia was considered resolved. The subject's hospital discharge details were not available. On day 49, study therapy was resumed. On day 89, 12 days post the 6th dose of nivolumab, the subject was hospitalized with a fever (101.5°F) and increased dyspnea. Laboratory test results on day 89 included high white blood cell count. Chest x-ray showed complete right upper lobe consolidation and atelectasis, and probable increased volume loss over the right upper lobe compared with a prior chest radiograph. A serious adverse event of pneumonia with day 89 onset was reported, which was considered by the Investigator to be not related to the study therapy and the subject was started on intranasal budesonide daily (dose unknown), piperacillin/tazobactam, and vancomycin. On day 91, a chest x-ray showed bilateral pulmonary infiltrates, and right upper lobe collapse. On day 92 a lower bilateral doppler test showed no evidence of deep vein thrombosis and a chest x-ray showed right upper lobe collapse, bilateral pulmonary infiltrate consistent with an area of edema or pneumonia, and no evidence of pneumothorax. Study therapy was discontinued on day 92 due to the event of pneumonia, with the last dose received on day 77. The subject died on day 92 due to pneumonia, respiratory failure, and bradycardia. It is unknown whether an autopsy was performed.
Review comment: The information provided supports the reported cause of death (pneumonia), given the clinical history including episode of improvement on antibiotics and the characteristics on imaging.
Patient ID: CA209063-28-63142
SEPTIC SHOCK (GRADE 5, REPORTED AS NOT DRUG RELATED, DAY 164)
60-year old male with stage IV squamous non-small cell lung carcinoma. The subject's relevant medical history included chronic obstructive pulmonary disease, prior radiotherapy, dyspnea on exertion, cough and sputum production, hypertension, and peripheral arterial disease of lower limbs. The patient was a

current smoker. Subject was discontinued from study therapy due to fatigue, with the last dose received on day 71. On day 104, 33 days post the 6th dose of nivolumab, subject presented with 4 days of increased dyspnea, cough, and sputum production. The subject had one day of fever on day 104. Subject was hospitalized. CT scan showed no progression and no infiltrative pneumonia. On day 105, following a diagnosis of septic shock, subject was started on tobramycin, nefopam and intravenous (IV) hydrocortisone 200 mg and he became afebrile (temperature not provided). A brain CT showed normal results and no lesion, and a lumbar puncture showed no carcinomatous meningitis. On day 106 ((b) (6)), chest x-ray showed a pleural effusion and atelactasis, the subject's antibiotic regimen was changed to ciprofloxacin and piperacillin-tazobactam. Day 107 IV hydrocortisone to prednisone 20 mg oral. An adrenocorticotropic hormone (ACTH) level drawn that day was < 15 pg/mL (reference range: 0-52 pg/mL). On day 108 ((b) (6)), prednisone was increased to 40 mg (reason not provided). TSH level was 2.97 mU/L. On day 109 the antibiotic therapy was switched to ceftriaxone (blood culture results not provided). On day 113 septic shock was considered resolved and the subject was discharged from the hospital. On day 125, 54 days post the 6th dose of nivolumab subject became hypotensive (80/50 mmHg). Cardiac ultrasound scan showed a pericardial effusion of 0.7 cm and the subject was noted to have atrial fibrillation and treatment with heparin, amiodarone and betaxolol was initiated. Patient was diagnosed with pericarditis (grade 3). On Day 158 patient had pulmonary embolism (Grade 2) and subject received treatment with fondaparinux. On Day 164 subject was placed on ceftriaxone, aminoglycoside antibiotics (unspecified) and oxygen therapy after being admitted for what appears to have been an abscess with "collection of pus was unsuccessful via puncture on the right shoulder." On Day 167 patient again experienced pyrexia with hypotension (temperature and blood pressure details not available) with negative cultures and was switched to ciprofloxacin and piperacillin-tazobactam therapy and received morphine and midazolam. On day 170, the subject died due to septic shock. It is not known whether an autopsy was performed.

Reviewer comment: The information provided supports death due to infectious etiology, ie septic shock, although there are confounding factors such as pulmonary embolism.

Patient ID: CA209063-35-63124

ISCHAEMIC STROKE (GRADE 5, REPORTED AS DRUG RELATED, DAY 41)

74-year old female with stage IV squamous non-small cell lung carcinoma and metastases in lymph nodes and adrenal glands. The subject's relevant medical history included: hypertension, heart attack, pulmonary embolism, left thoracic pain, history of radiation therapy to the thoracic spine with sequelae of radiation esophagitis, history of vertebral metastases status-post percutaneous kyphoplasty and vertebrectomy with fixation from T5−T10, and temporal CNS bleeding attributed to a fall 2 months prior to enrolling into the study. The subject was a former smoker. On day 15, 14 days post the 1st dose of nivolumab, laboratory test results showed a further increase in creatinine and an elevated C-reactive protein (CRP) of 109.5 mg/L (reference range: 0-5 mg/L), and the subject was hospitalized for evaluation of elevated creatinine. Grade 2 acute renal failure was reported, which the Investigator considered related to the study therapy. The subject was treated with hydration and electrolyte supplementation, and the creatinine level improved. On the day of hospitalization (day 15), the subject also developed a paresis of the right arm and both legs, which was reported as a serious adverse event of Grade 2 peripheral nerve paresis and a nonserious adverse event of Grade 4 polyneuropathy, both considered related to the study therapy. Autoimmune and paraneoplastic etiologies of the paresis were also considered possible. The subject also developed signs of livedo reticularis, and the CRP remained elevated at 134 mg/L. Electromyography showed severe axonal sensomotoric polyneuropathy with signs of acute denervation. There were no ganglioside−antibodies or IgM−antibodies against Myelin−associated−Glykoprotein (MaG) detected. The rheumatology consult suspected an immune complex vasculitis or light chain associated neuritis based on evaluation including blood work. Subjects was started on steroids on Day 18 and on Day 20 showed a significant improvement of all her symptoms, and the CRP had lowered to 28.2 mg/L. Within the next few days, the subject again had paresis. Rheumatologic laboratory results on day 25 revealed the following: no antiphospholipid antibodies were detected; ANCA ELISA profile negative; ANA positive at 1:1000 dilution (reference range <1:100); ANA immunoblot profile positive for anti−Ro52. Apheresis was performed, treatment with intravenous immunoglobulin (reported as verbatim term Kiovig) was initiated and gamma globulin was received until day 27. On day 29 ((b) (6)), a CT angiogram

showed pulmonary embolism. A skin biopsy performed on day 29 was suspicious for cryoglobulinemia but showed no sign of vasculitis. On day 31 the subject was treated with IV cyclophosphamide 1000 mg x1 for the paresis; however, her neurological status remained unchanged. Additional treatments included etoricoxib, zopiclone, pregabalin, and tramadol. The subject declined any additional treatments for her paresis. The study therapy was discontinued on day 31 due to the event of polyneuropathy, with the last dose received on day 1. On day 41, 40 days post the 1st dose of nivolumab, the investigator reported a serious adverse event of ischemic stroke which was considered to be related to the study therapy. Best supportive care was initiated, and the subject died due to ischemic stroke on the same day (day 41). No known autopsy was conducted.
Reviewer comment: The information provided can support death due to ischemic stroke in the setting of an autoimmune phenomenon including vasculitis, which may have been drug related.
Patient ID: CA209063-9-63067
AORTIC ANEURYSM RUPTURE (GRADE 5, REPORTED AS NOT DRUG RELATED, DAY 82)
63-year old female with stage IV squamous non-small cell lung carcinoma and lymph node metastases. The subject's relevant medical history included abdominal aortic aneurysm, hypertension, history of pulmonary emboli, chronic back pain, and was a former smoker. On day 56 CT scan showed abdominal aortic aneurysm enlargement. On day 57 an adverse event of Grade 1 hypertension, which was considered by the Investigator to be not related to the study therapy, was reported. The subject's blood pressure (BP) was 140/90 mmHg (baseline: 122/72 mmHg on day -14. The subject did not receive treatment for the event of hypertension and no action was taken with regard to the study therapy. On day 70 the subject was evaluated by her vascular surgeon who determined that her aneurysm had increased from 4.9 cm to 5.4 cm in a period of 11 months and also determined 15% risk of rupture within next year. The subject did not undergo endo-vascular procedure due to the associated risks, anatomic location of the aneurysm and her co-morbidities. On day 82, 11 days post the 6th dose of nivolumab, the subject presented to an external hospital via ambulance due to severe abdominal pain. Abdominal CT scan showed aortic aneurysm rupture with significant bleed. The subject did not receive treatment for the event of aortic aneurysm rupture. On day 83, the subject died due to the event of aortic aneurysm rupture. It is not known whether an autopsy was performed.
Reviewer comment: The information provided supports death due to aortic aneurysm rupture, which had not been corrected due to subject's comorbidities and may not have been drug related.

An information request was sent to the applicant regarding patient CA209063-14-63035 with a fatal case of hypoxic pneumonia to rule out death due to pneumonitis. The applicant emphasized that the investigator's assessment in this patient was that pneumonia was the most appropriate reported term describing the direct cause of death. The applicant provided the following additional information:

Prior to the onset of this event, the subject had discontinued nivolumab due to documented disease progression. Twenty-two days after his last nivolumab dose, the subject developed a post-obstructive pneumonia, associated with a large (6.5 cm) left lung mass in the vicinity of the aortic arch. The clinical presentation (pyrexia, highly elevated CRP, and leukocytosis), as well as dense consolidation in almost the entire lower left lung, were consistent with pneumonia, and are not characteristic features typically associated with nivolumab-related pneumonitis. Furthermore, the right-sided lung infiltrates were not considered conclusive of pneumonitis in the context of the co-existing pneumonia and disease progression. The investigator stated "my conclusion is that the patient died from severe pneumonia that can be due either to an opportunistic infection or an immunoallergic reaction promoted by a rapidly evolutive tumor," and therefore, reported pneumonia as the direct cause of death. As an inflammatory

component to the pneumonia could not be completely excluded, the investigator considered the pneumonia as possibly drug-related."

Overall, the applicant's rationale for the fatal event in patient CA209063-14-63035 being unrelated to pneumonitis appears reasonable. Please see the paragraph below regarding the fatal cases of pneumonitis in Study MDX1106-03.

A total of 195 (63.7%) subjects died in MDX1106-03 with181 (59.2%) deaths due to disease progression. Five subjects died due to probable drug toxicity and 3 subjects due to ischemic cardiomyopathy (1 patient) and unknown cause (2 patients). The 5 deaths likely related to the drug all occurred in patients with pneumonitis. The applicant states that sufficient corticosteroids were not started when symptoms of pneumonitis, such as dyspnea, were first recognized in these patients because pneumonitis was not an expected toxicity at the time these events occurred. Subsequently, treatment guidelines for the management of pneumonitis recommending the early initiation of corticosteroids were implemented throughout the clinical program.

Severe and potentially fatal cases of pneumonitis, although rare, are possible with administration of nivolumab, especially in situations where corticosteroids treatment is delayed. Please also see section 7.3.2.

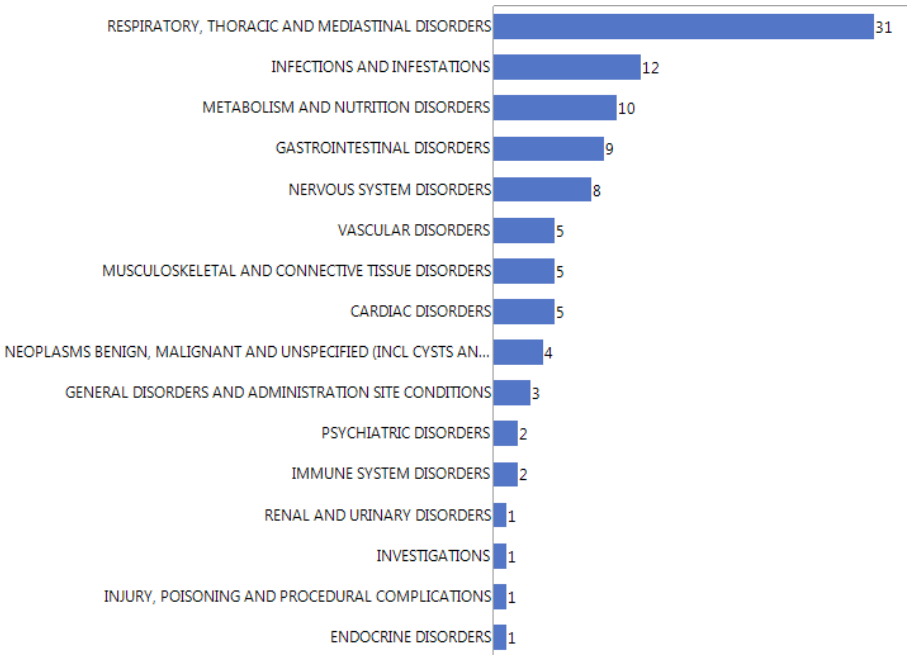
7.3.2 Nonfatal Serious Adverse Events

Overall, 120 nonfatal SAEs occurred in 66 of 117 (56.4%) patients (data up to 100 day follow up period). The most common nonfatal SAEs occurring in 31 (26.5%) of patients were "respiratory, thoracic, and mediastinal disorders" per MedDRA SOC and included dyspnea (8 patients), pneumonitis, pneumonia, hypercalcemia, and chronic obstructive pulmonary disease (COPD, 6 patients each; Figure 23). Of the 66 patients, the majority were male (66.7%) and white (84.8%). The majority (87.5%) of the 120 nonfatal SAEs were reported as recovering/resolved. Most of the nonfatal SAEs occurred during the 30 follow up period (39.2%) or on treatment (38.3%).

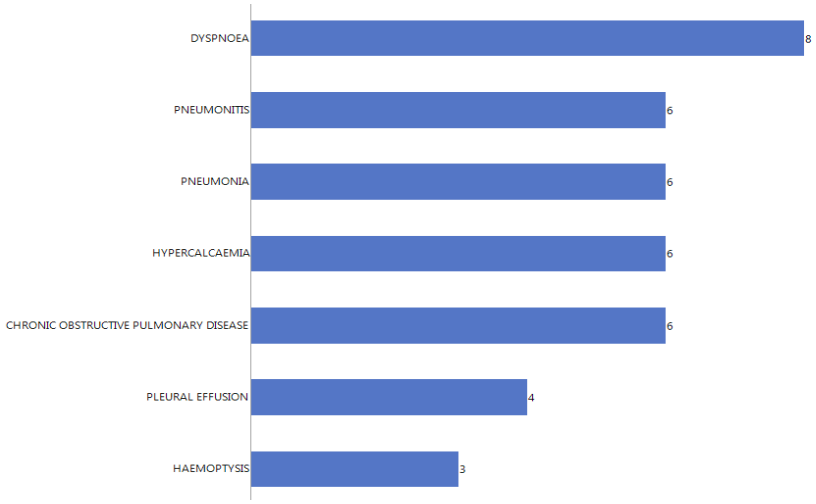
Overall, many of the nonfatal SAEs appear to have been related to underlying disease (e.g., pneumonia, COPD exacerbation) and immune-related events (pnumonitis).

Figure 23. Nonfatal serious adverse events in Study CA209063

MedDRA System Organ Class



MedDRA Preferred Term (> 2 patients)



Reviewer analysis, dataset ADSL

Table 31. Study drug related nonfatal serious adverse events in Study CA209063

Subject ID	Event (MedDRA PT)	Grade	Outcome
CA209063-10-63086	ADRENAL INSUFFICIENCY PNEUMONITIS	3 3	RECOVERED/RESOLVED RECOVERED/RESOLVED
CA209063-12-63111	PNEUMONITIS	2	RECOVERED/RESOLVED
CA209063-12-63117	PNEUMONITIS	3	RECOVERED/RESOLVED
CA209063-14-63022	HERPES ZOSTER	3	RECOVERED/RESOLVED
CA209063-32-63054	PNEUMONITIS	3	RECOVERED/RESOLVED
CA209063-34-63074	HYPERSENSITIVITY	4	RECOVERED/RESOLVED
CA209063-35-63124	PERIPHERAL NERVE PARESIS	2	NOT RECOVERED/NOT RESOLVED
CA209063-7-63025	PNEUMONITIS	3	RECOVERED/RESOLVED
CA209063-7-63026	PNEUMONITIS	3	RECOVERED/RESOLVED
CA209063-9-63055	ANAPHYLACTIC REACTION	3	RECOVERED/RESOLVED
CA209063-9-63068	DIARRHEA	3	RECOVERED/RESOLVED
Reviewer analysis, ADSL dataset			

Overall, the types, frequency, and severity of nonfatal SAEs reported in Study MDX1106-03 were generally consistent with those reported in Study CA209063.

7.3.3 Dropouts and/or Discontinuations

A total of 39 (33%) of patients discontinued due to AEs with 7 cases most likely not drug related (e.g., disease progression) (Table 32). The outcome of AEs leading to discontinuation in 33 patients (32 derived from dataset ADAE + 1 extracted from patient narrative) were: 20 recovered/resolved, 9 were fatal, 3 recovered/resolved with sequalea, and 1 not recovered/not resolved (

Table 33). The most common AE leading to discontinuation (excluding disease progression) was pneumonitis in 5 cases. All 5 cases of pneumonitis appear to have resolved.

In Study MDX1106-03, at least 1 AE leading to discontinuation was reported in 57 (18.6%) of all treated subjects. The most frequently reported AE leading to discontinuation was pneumonitis (8 subjects, 2.6%).

Table 32. Adverse events leading to drug discontinuation in Study CA209063

ADVERSE EVENT	N
MALIGNANT NEOPLASM PROGRESSION	5
PNEUMONITIS	5
DYSPNOEA	2
FATIGUE	2

HYPERCALCAEMIA	2
PNEUMONIA	2
ABDOMINAL PAIN	1
ADRENAL INSUFFICIENCY	1
ANAPHYLACTIC REACTION	1
AORTIC ANEURYSM RUPTURE	1
ATRIAL FIBRILLATION	1
COGNITIVE DISORDER	1
CONFUSIONAL STATE	1
DECREASED APPETITE	1
DIARRHOEA	1
HYPERSENSITIVITY	1
MOTOR DYSFUNCTION	1
PERFORMANCE STATUS DECREASED	1
PLEURAL EFFUSION	1
POLYNEUROPATHY	1
PULMONARY EMBOLISM	1
PULMONARY HAEMORRHAGE	1
RASH	1
SEPTIC SHOCK	1
SUPERIOR VENA CAVA SYNDROME	1
TOXICITY TO VARIOUS AGENTS	1
UNASSIGNED	1
VOMITING	1

In Study CA209063, dose delays occurred in 27% of patients. The median duration of dose delays was 14.0 days (6 to 56). A dose was considered as actually delayed if the delay is exceeding 3 days. No patients required infusion rate reduction. The protocol called for discontinuation if the dose was delay more than 6 weeks and one patient had a delay without discontinuation more than 6 weeks. (b) (4) an information request was sent to provide data in NSCLC patients who required a dose delay of more than 6 weeks and were re-challenged with nivolumab. Seven patients in separate NSCLC studies CA209017 and CA209057 had dosing delays ≥ 8 weeks from last dose. Among these 7 patients, 3 (Patient ID CA209017-17-17029, CA209057-83-57565, and CA209057-108-57584) had dosing delayed due to investigator-assessed drug-related adverse reactions, with length of delay for these 3 patients ranging from 14.7 weeks to 17.3 weeks.

Table 33. Outcomes of adverse events leading to dose discontinuation

Adverse Event Outcome	Adverse Event	Grade	Investigator attribution	N
FATAL	AORTIC ANEURYSM RUPTURE	5	NOT RELATED	1
	MALIGNANT NEOPLASM PROGRESSION	5	NOT RELATED	5
	PERFORMANCE STATUS DECREASED	5	NOT RELATED	1
	PNEUMONIA	5	NOT RELATED	1
	SEPTIC SHOCK	5	NOT RELATED	1
NOT RECOVERED/NOT RESOLVED	MOTOR DYSFUNCTION	3	NOT RELATED	1
RECOVERED/RESOLVED	ABDOMINAL PAIN	3	NOT RELATED	1
	ADRENAL INSUFFICIENCY	3	RELATED	1
	ANAPHYLACTIC REACTION*	3	RELATED	1
	ATRIAL FIBRILLATION	3	NOT RELATED	1
	COGNITIVE DISORDER	2	NOT RELATED	1
	CONFUSIONAL STATE	3	NOT RELATED	1
	DIARRHEA	3	RELATED	1
	DYSPNEA	3	NOT RELATED	1
	HYPERCALCEMIA	1	NOT RELATED	1
	HYPERCALCEMIA	4	NOT RELATED	1
	HYPERSENSITIVITY	4	RELATED	1
	PLEURAL EFFUSION	3	NOT RELATED	1
	PNEUMONITIS	3	RELATED	5
	PULMONARY EMBOLISM	3	NOT RELATED	1
	PULMONARY HAEMORRHAGE	3	NOT RELATED	1
	VOMITING	3	NOT RELATED	1
RECOVERED/RESOLVED WITH SEQUELAE	DECREASED APPETITE	3	NOT RELATED	1
	DYSPNEA	3	NOT RELATED	1
	SUPERIOR VENA CAVA SYNDROME	4	NOT RELATED	1
All				**33**

Reviewer analysis, dataset ADAE and patient narratives.
Seven events had outcomes missing in dataset ADAE using [AEOUT] variable.
*Review of the narrative summary of the event did not show a clear case of an anaphylaxis reaction.

7.3.5 Submission Specific Primary Safety Concerns

For characterization of likely immune-mediated adverse events in Study CA209063, FDA defined a case as one requiring the use of systemic corticosteroids with no clear alternative etiology. Using this case definition, several events were identified (

Table 34).

Table 34. Immune-mediated adverse events in Study CA209063

ADVERSE EVENT	Highest Grade	No Patients (%)
PNEUMONITIS	3	7 (5.9)
HYPOTHYROIDISM	2	5 (4.2)
MOTOR DYSFUNCTION	3	2 (1.7)
THYROIDITIS/HYPERTHYROIDISM	2	2
RASH	2	2
ADRENAL INSUFFICIENCY	3	1 (1.0)
DIARRHEA/COLITIS	3	1
RENAL FAILURE	2	1
VASCULITIS	3	1
Total		**22 (19)**
Reviewer analysis.		

Key immune-mediated adverse events in Study CA209063

Immune mediated pneumonitis occurred in seven patients, comprised of five Grade 3 and two Grade 2 cases. The median time to onset was 3.3 months (range: 1.4-13.5 months). All seven patients discontinued treatment for either pneumonitis (5 patients) or another event and all seven patients had complete resolution of pneumonitis following high-dose corticosteroids defined as 40 mg prednisone equivalents per day. FDA issued an information request to BMS to provide data on the safety of nivolumab re-challenge in patients with advanced NSCLC whose treatment is withheld due to pneumonitis. BMS's review of their completed or ongoing NSCLC trials within the nivolumab program identified 7 patients who were re-challenged with nivolumab after Grade 1 or 2 pneumonitis without reported worsening or recurrence of pneumonitis. At the time of this review, these patients either were continuing on nivolumab treatment, or had discontinued due to reasons other than pneumonitis. An additional 5 NSCLC subjects were identified who were re-challenged with nivolumab after Grade 1 or 2 pneumonitis and experienced pneumonitis worsening or recurrence, of whom 4 discontinued due to the recurrence (1 subject developed recurrence after prior discontinuation for disease progression). Overall, these data support attempting nivolumab re-challenge with careful monitoring and follow up in advanced NSCLC patients upon resolution of Grade 1 or 2 pneumonitis.

Immune-mediated colitis (Grade 3) occurred in one patient. The time to onset in this patient was 6.7 months. The patient received high-dose corticosteroids and permanently discontinued treatment. The event was reported as resolved following discontinuation of therapy.

Immune-mediated renal dysfunction (Grade 2) occurred in one patients. The time to onset in this patient was 0.8 months. The patient received high-dose corticosteroids and treatment was withheld. The patient discontinued due to disease progression prior to receiving additional treatment with nivolumab. Immune-mediated renal dysfunction was reported as ongoing.

Hypothyroidism (Grade 1 or 2) occurred in five patients. The median time to onset for these five cases was 4.1 months (range: 1.4-4.6 months). All five patients with hypothyroidism received levothyroxine with resolution of hypothyroidism in one patient with allowing discontinuation of levothyroxine.

Hyperthyroidism occurred in two patients. One patient experienced Grade 2 hyperthyroidism 5.2 months after the first dose of treatment, requiring management with high-dose corticosteroids and methimazole. Thyroid laboratory tests returned to normal 4.7 months later.

AEs possibly related to hypersensitivity/infusion reactions were reported in 7 (6%) patients in CA209063 which included 3 Grade 3-4 events: Grade 3 anaphylactic reaction (Subject CA209063-9-63055), Grade 4 hypersensitivity (Subject CA209063-34-63074), and Grade 3 bronchospasm (CA209063-15-63127, 2 events). One possible hypersensitivity/infusion reaction was reported in the SQ NSCLC 3 mg/kg cohort in MDX1106-03; Grade 1 bronchospasm considered not drug-related by the investigator. In CA209063, the median time to onset of possible hypersensitivity/infusion reactions was 2.1 weeks (range: 0.1 to 27.9 weeks). All Grade 3-4 events in CA209063 were managed with immunosuppressive medication (corticosteroids in all cases). All cases were reported as resolved in Study CA209063. The median time to resolution was 0.1 weeks.

FDA requested further information on the Grade 3 anaphylactic reaction (CA209063-9-63055). BMS provided the following:

> Subject CA209063-9-63055 was a 59-year old male with stage IV squamous non-small cell lung carcinoma and metastases in lymph nodes.
>
> The subject's relevant medical history included possible anaphylactic reaction to docetaxel, asthma (since childhood). The pre-treatment events included mild cough. The subject received treatment with diphenhydramine and doxycycline since day -10 (23-Apr-2013).
>
> On his baseline visit, day -7 (26-Apr-2013), the subject's vital signs were notable for a blood pressure (BP) of 119/36 mmHg and a heart rate (HR) of 95.
>
> On day 1 (03−May−2013), the day of the first nivolumab dose, approximately 15 to 20 minutes after initiation of the infusion, the subject reported shortness of breath, throat constriction and breathing difficulties. The subject's wife reported that the

subject had previously experienced a "similar reaction to docetaxel." Oxygen saturation on room air was 91% and vital signs were: BP 105/56 mmHg, HR 99, respiratory rate of 16 and temperature of 36.9 C. The infusion of nivolumab was stopped (total infusion 28 minutes) and the subject was started on treatment with intravenous (IV) normal saline and received 2 liters of oxygen via nasal cannula. He also received treatment with IV diphenhydramine, IV methylprednisolone 125 mg, and famotidine 20 mg, followed by salbutamol nebulizer treatment. A serious adverse event of Grade 3 anaphylactic reaction (recorded as verbatim term anaphylaxis), considered by the Investigator to be related to the study therapy, was reported, resolution of the event on the same day (day 1). The study therapy was discontinued due to the event of anaphylactic reaction, with the last dose received on day 1 (03-May-2013). The event of cough was ongoing and the subject continued to receive treatment with diphenhydramine and as of the database lock, the subject had withdrawn consent to further participation and data collection for this study.

It is unclear whether his case was a true anaphylactic reaction as this was the first dose of nivolumab, no systemic epinephrine was administered, and there was no re-challenge.

Overall, immune-mediated adverse events associated with nivolumab can be potentially serious but appear to be manageable with prompt recognition and treatment with corticosteroids ±treatment drug discontinuation/interruption.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

AEs occurring in ≥10% of patients (up to 30 day follow up) in Study CA209063 are shown in Table 35.

Table 35. Adverse events occurring in ≥10% of patients in Study CA209063

Preferred Term (MedDRA 17.0)	Events	All Grades, N (%)		Grade 3-4 N (%)
Fatigue	108	58	49.6	8 (6.8)
Dyspnea	70	44	37.6	10 (8.5)
Decreased appetite	56	41	35.0	3 (2.6)
Cough	50	37	31.6	2 (1.7)
Nausea	48	34	29.0	2 (1.7)
Constipation	31	28	23.9	0
Asthenia	39	22	18.8	2 (1.7)
Vomiting	27	22	18.8	1 (0.9)

Diarrhea	47	21	18.0	3 (2.6)
Anemia	29	20	17.0	3 (2.6)
Pyrexia	22	20	17.0	0
Abdominal pain	20	15	12.8	2 (1.7)
Weight decreased	17	15	12.8	1 (0.9)
Edema peripheral	15	14	12.0	1 (0.9)
Rash	17	14	12.0	1 (0.9)
Arthralgia	15	13	11.1	0
Pruritus	18	13	11.1	1 (0.9)
Hypercalcemia	18	12	10.3	4 (3.4)
Pain	13	12	10.3	3 (2.6)
Reviewer analysis, dataset ADAE.				

In Study CA209063, grade 3-4 events occurred in 72 (61.5%) patients, up to 100 days follow up period. Grade 3-4 AEs occurring in greater than 2 subjects are shown in Table 36.

In Study MDX1106-03, the most frequently reported any grade select AEs across all tumor types (n=306) were diarrhea (34.3%), rash (24.2%), and pruritus (18.3%). The most frequently reported Grade 3 to 4 select AEs were renal failure acute (2.3%), ALT increased (1.6%), AST increased (1.6%), pneumonitis (1.3%).

Table 36. Grade 3-4 adverse events in >2 subjects in Study CA209063 (n=117)

Adverse event	**N**	**%**
DYSPNEA	12	10.3
FATIGUE	8	6.8
HYPONATRAEMIA	7	6.0
PNEUMONIA	7	6.0
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	5	4.3
HYPERCALCAEMIA	5	4.3
PNEUMONITIS	5	4.3
DEHYDRATION	4	3.4
PAIN	4	3.4
PLEURAL EFFUSION	4	3.4
ANEMIA	3	2.6
ASTHENIA	3	2.6
DECREASED APPETITE	3	2.6
DIARRHEA	3	2.6
Reviewer analysis, dataset ADAE		

7.4.2 Laboratory Findings

Key laboratory findings in Study CA209063 are shown in Table 37. Lymphopenia and hyponatremia were two Grade 3-4 laboratory abnormalities with worsening in ≥10 of patients. Anemia of any Grade (shift from baseline) occurred in 28.1% and in most cases was low grade with the decrease in hemoglobin levels from baseline largely clustering within 0.7 quantile of (hemoglobin trial minimum/LLN) plotted against (hemoglobin baseline/LLN) (Figure 24).

Table 37. Laboratory abnormalities increased from baseline in ≥10% of patients for all Grades or ≥2% for Grades 3-4 in Study CA209063

Test	Percentage of Patients with Worsening Laboratory Test from Baseline	
	All Grades	Grades 3-4
Lymphopenia	47.4	15.8
Hyponatremia	37.7	9.6
Anemia	28.1	2.6
Increased creatinine	21.9	0
Hypercalcemia	20.2	2.6
Hypokalemia	20.2	2.6
Hypomagnesemia	19.6	0
Hypocalcemia	17.5	1.8
Hyperkalemia	17.5	4.4
Increased AST	15.9	0.9
Increased alkaline phosphatase	14.4	0
Thrombocytopenia	14.0	0
Increased ALT	11.5	0

Range 111 to 114 patients.
Combined reviewer and applicant analyses. Dataset [LB].

FDA analysis of liver laboratory abnormalities identified no clear cases of Hy's law. The vast majority of the peak laboratory values in liver function tests in Study CA209063 were ≤ 3 x ULN for AST, ALT, and alkaline phosphatase and ≤ 2 x ULN for total bilirubin (Figure 25).

Figure 24. Shift plot for hemoglobin laboratory values in Study CA209063 expressed as trial minimum (Y axis) versus baseline (X axis), all normalized to lower limit of normal (LLN). **[reviewer analysis, dataset LB]**

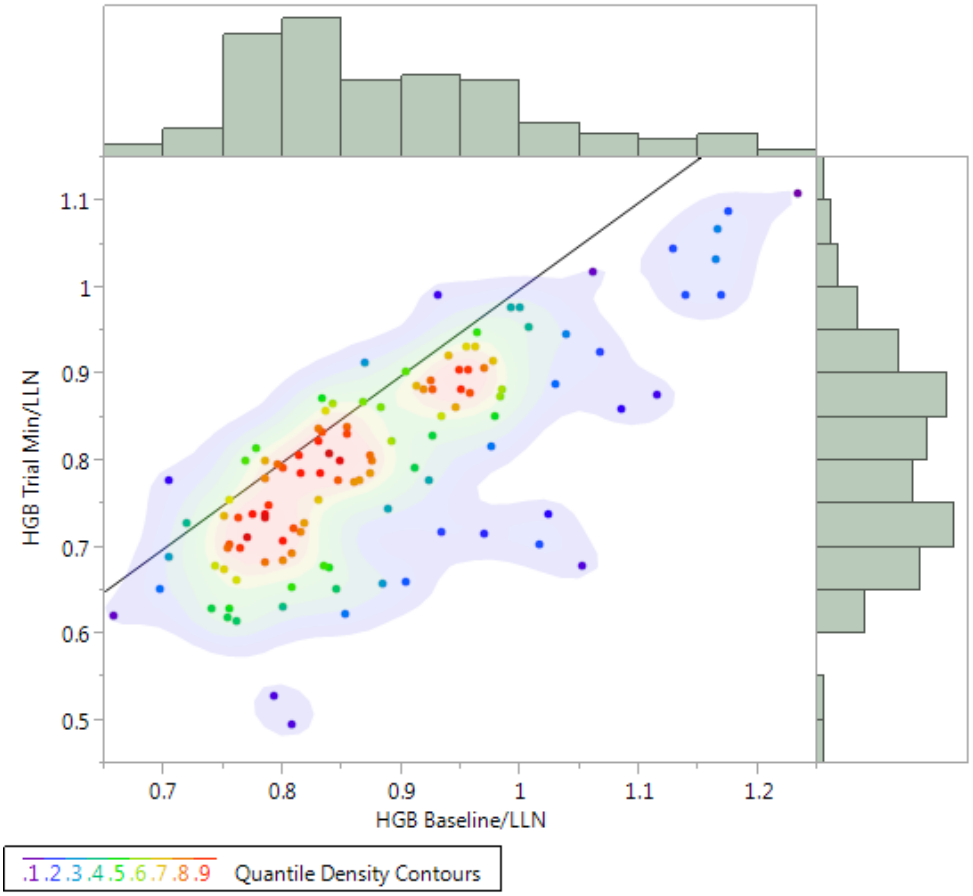
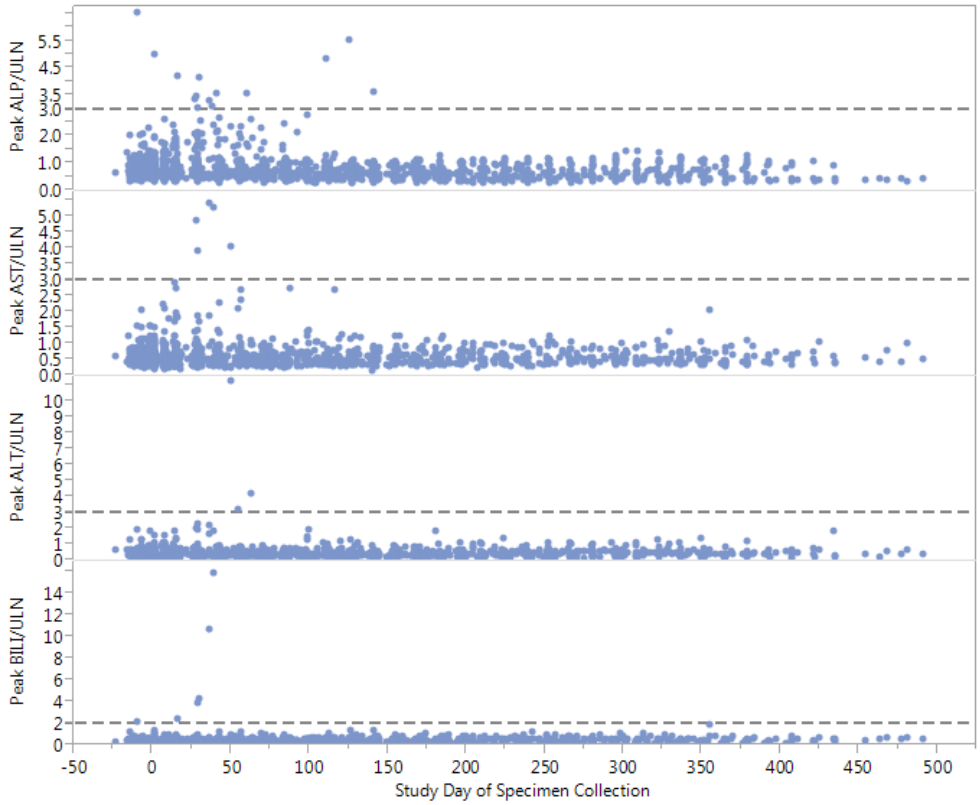


Figure 25. Peak liver function laboratory values in Study CA209063



7.4.3 Vital Signs

Vital signs were monitored and recorded before, during, and after each infusion of nivolumab in Study CA209063. A review of these data did not identify any clinically significant safety concerns.

7.4.4 Electrocardiograms (ECGs)

ECGs were not formally evaluated in Study CA209063. QTc prolongation was evaluated in Sub-Study CA209010, a randomized, double-blind, 3-arm dose-ranging trial (with 0.3, 2, and 10 mg/kg nivolumab) in patients with advanced/metastatic renal cell carcinoma with a clear-cell component who had received prior treatment with at least 1 anti-angiogenic therapy in the advanced/metastatic setting. Total of146 patients contributed data to the ECG analysis. Results of central tendency analysis conducted by the applicant indicated no dose response for QTcF or change in QTcF (ΔQTcF) on Day 1 of Cycles 1 or 7. No uncorrected QT interval exceeded 483 msec during the study and the longest QT interval was in the 0.3 mg/kg dose group. There was no dose response for changes from baseline in PR interval, QRS interval, or HR on either Day 1 or Day 7. Results of categorical analysis conducted by the applicant indicated that no patients had

QTcF intervals or ΔQTcF that exceeded the prespecified ranges considered borderline or prolonged. No subject had a QTcF interval > 470 msec or a ΔQTcF > 45 msec. The nivolumab concentration-response analysis conducted by the applicant indicated no relationship between QTcF change from baseline and nivolumab concentration. Similar to these results, there was no association (slope = 0) between the predicted mean maximum ΔQTcF and mean maximum nivolumab concentration according to the applicant. Results for PR and QRS intervals were similarly unremarkable per applicant's analyses.

7.4.5 Special Safety Studies/Clinical Trials

Please refer to section 7.4.4 (ECGs) for information on Sub-Study CA209010.

7.4.6 Immunogenicity

Immunogenicity was an exploratory endpoint in Study CA209063. Blood samples were collected and evaluated for the presence of antibodies to nivolumab (anti-drug antibodies [ADA]) using an ECL immunoassay in human serum. The presence of neutralizing antibodies was also evaluated in ADA-positive samples using a cell-based functional assay. During treatment, anti-nivolumab ADAs were detected in 12/101 (11.9%) patients with evaluable ADA data at baseline and post baseline, of whom no patients were persistent positive (ADA positive sample at 2 or more sequential timepoints at least 8 weeks apart). No samples were positive for neutralizing antibodies.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no clear relationship between the incidence of select AEs and the dose of nivolumab in Study MDX1106-03. Although there were numerically more treatment-related Grade 3 to 4 select AEs in patients receiving 10 mg/kg, no single category of these AE seemed to drive that finding according to analyses conducted by the applicant.

7.5.2 Time Dependency for Adverse Events

Please refer to discussion on immune-mediated adverse events.

7.5.3 Drug-Demographic Interactions

The majority (73%) of patients in Study CA209063 were male. The results of an exploratory analysis of common AEs (up to 30 day follow up) in females versus males are shown in Table 38. All cases of pneumonitis were observed in males.

Table 38. Exploratory analysis of drug-gender interactions

Adverse event (Preferred Term)	ChiSquare	Prob>ChiSq	M	F	RR (F vs M)
HEADACHE	6.2857	0.0122			4.7
NAUSEA	5.9725	0.0145			2.4
MUCOSAL INFLAMMATION	5.8667	0.0154			6.6
BLOOD ALKALINE PHOSPHATASE INCREASED	5.1858	0.0228			N/A (all 2 cases F)
BURNING SENSATION	5.1858	0.0228			N/A (all 2 cases F)
DEPRESSION	5.1858	0.0228			N/A (all 2 cases F)
PALPITATIONS	5.1858	0.0228			N/A (all 2 cases F)
MUSCULOSKELETAL PAIN	5.1124	0.0238			N/A (all 8 cases M)
ANAEMIA	4.5933	0.0321			2.7
DYSGEUSIA	3.9190	0.0477			8.0
PNEUMONITIS	3.8343	0.0502			N/A (all 7 cases M)
VOMITING	3.2809	0.0701			2.2

F, female; M, male; RR, relative risk
NOTE: Exploratory analysis. Chi-square statistics used for ranking only.
Reviewer analysis. Dataset [ADAE].

The overall safety profile of nivolumab at 3 mg/kg appeared to be similar between patients ≥ 65 years of age and those < 65 years of age (final CSR). A numerical imbalance was observed between patients ≥ 65 years (n = 59) and < 65 years (n = 58) for several AEs as follows (2-fold difference in events reported by ≥ 5 patients in any group):

- Events (all grades) reported more frequently in subjects ≥ 65 years than < 65 years included chronic obstructive pulmonary disease (8.5% vs. 0), myalgia (15.3% vs. 3.4%), bronchitis (11.9% vs. 1.7%), blood creatinine increased (11.9% vs. 5.2%), and hypertension (8.5% vs 3.4%).
- Events (all grades) reported less frequently in subjects ≥ 65 years than < 65 years included pain (6.8% vs. 13.8%), pneumonia (5.1% vs. 10.3%), and weight decreased (6.8% vs. 15.5%).

- Grade 3-4 fatigue was reported more frequently in subjects ≥ 65 years (10.2%) than < 65 years (3.4%).

Nearly all patients were white; therefore, clinically meaningful differences in safety across racial subgroups could not be analyzed.

7.5.4 Drug-Disease Interactions

All patients in Study CA209063 were squamous cell histology and advanced stage; therefore, the population was considered homogeneous in terms of known/reported disease status for safety evaluations.

7.5.5 Drug-Drug Interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity.

7.6.2 Human Reproduction and Pregnancy Data

Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of nivolumab have not been established in pediatric patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no information on overdosage with nivolumab.

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

N/A.

9 Appendices

9.1 Literature Review/References

1. What are the key statistics about lung cancer? American Cancer Society 2014.
2. Lung Cancer Fact Sheet. American Lung Association2014.
3. Sadiq AA, Salgia R. MET as a possible target for non-small-cell lung cancer. J Clin Oncol 2013;31:1089-96.
4. Oxnard GR, Binder A, Janne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 2013;31:1097-104.
5. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. J Clin Oncol 2013;31:1039-49.
6. Huang X, Yang Y. Targeting co-stimulatory pathways in gene therapy. Frontiers in microbiology 2011;2:202.
7. Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol 2013;14:1212-8.
8. Amin A, White RL, Jr. High-dose interleukin-2: is it still indicated for melanoma and RCC in an era of targeted therapies? Oncology (Williston Park, NY) 2013;27:680-91.
9. Champiat S, Ferté C, Lebel-Binay S, Eggermont A, Soria JC. Exomics and immunogenics: Bridging mutational load and immune checkpoints efficacy. Oncoimmunology 2014;3.

9.2 Labeling Recommendations

Critical labeling recommendations included:

- Section 1: recommended that indication be for metastatic squamous NSCLC with progression on or after platinum-based chemotherapy (017 population)
- Section 5: described the immune-mediated pneumonitis, colitis, hepatitis, nephritis/renal dysfunction, hypothyroid and hyperthyroidism, and other immune-mediated reactions in NSCLC patients
- Section 6: Adverse reactions and laboratory abnormalities based on patients enrolled in single arm 063 trial irrespective of causality and attribution
- Section 14: Include OS data from 017 trial. Refine demographics to better describe % of patients with recurrent IIIB disease. Remove (b) (4) Remove any discussion o (b) (4) .

9.3 Advisory Committee Meeting

The BLA was not presented to the Oncologic Drugs Advisory Committee (ODAC) because the application did not raise significant efficacy or safety issues for the proposed indication, and outside expertise from ODAC was not considered necessary since there were no controversial issues that would benefit from advisory committee discussion.

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

/s/

DICKRAN G KAZANDJIAN
03/02/2015

SEAN N KHOZIN
03/02/2015

LIJUN ZHANG
03/02/2015

SHENGHUI TANG
03/02/2015

GIDEON M BLUMENTHAL
03/02/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125527 **Applicant: Bristol-Myers Squibb** **Stamp Date:**

Drug Name: Nivolumab **NDA/BLA Type: BLA type 9**

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			
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			
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?				pending
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			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
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).	1			
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 & CA209001 Study Title: A Phase 1, open-label, multicenter, multidose, dose escalation study of BMS-936558 in subjects with selected advanced or recurrent malignancies & A Phase 1, open-label, dose-escalation, safety and pharmacokinetic study of MDX-1106 in patients with selected refractory or relapsed malignancies	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 129 NSCLC & 12 NSCLC Arms: 3 & 4 Location in submission: 5.3.3.2				
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 CA209063 Indication: 3rd line Squamous NSCLC Pivotal Study #2 CA209017 Indication: 2nd line Squamous NSCLC	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			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	n/a			
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			Study CA209010 addresses this
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			In summary of clinical safety
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?	n/a			
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			MedDRA versions 17 and 16.1 used

[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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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			Hepatic
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Safety Narratives for Deaths, Related SAEs, Discontinuations Due to AEs, and Other Significant Medical Events have been included
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)?	n/a			
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	n/a			
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	n/a			
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	X			

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
	clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? _____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.

Reviewing Medical Officer Date

Clinical 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/

DICKRAN G KAZANDJIAN
01/27/2015

SEAN N KHOZIN
01/27/2015

GIDEON M BLUMENTHAL
01/27/2015

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

BLA Number: 125527 **Applicant: BMS** **Stamp Date: 12/22/2014**

Drug Name: Nivolumab **NDA/BLA Type: Efficacy Supp**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			SCE replaced ISE.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical 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.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No efficacy interim analysis planned
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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/s/

LIJUN ZHANG
01/13/2015

SHENGHUI TANG
01/14/2015