Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. N Engl J Med 2015;373:123-35. DOI: 10.1056/NEJMoa1504627

15-04627 - Nivolumab versus Docetaxel in Previously Treated Patients with Advanced Squamous Non-Small Cell Lung Cancer

This supplement contains the following items:
1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

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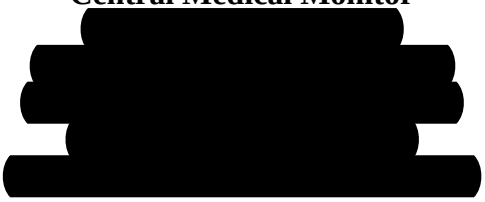
Date: 12-Jun-2012

Clinical Protocol CA209017

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

Central Medical Monitor



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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	12-Jun-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209017

Protocol Title: Protocol CA209017: An Open-label Randomized Phase III Trial of BMS-936558 versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer (NSCLC)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): For subjects randomized to BMS-936558, BMS-936558 will be 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 will be dosed intravenously over 60 minutes at 75mg/ m² every 3 weeks until disease progression, unacceptable toxicity or other reasons specified in the protocol.

Study Phase: 3

Research Hypothesis: BMS-936558 improves ORR and/or increases OS as compared with docetaxel, in squamous cell NSCLC subjects treated with prior platinum-based doublet chemotherapy.

Objective(s):

Primary Objective: To compare the ORR and OS of BMS-936558 versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy.

Secondary Objectives: Secondary objectives include the following:

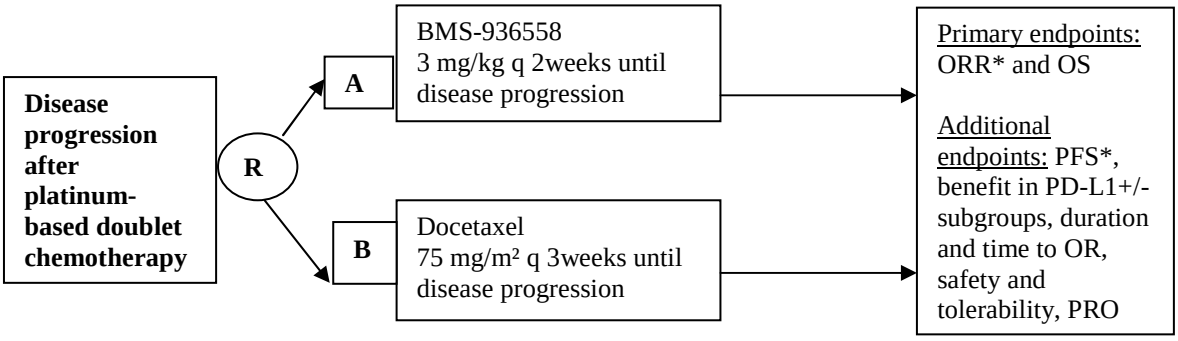
- To compare the progression-free survival (PFS) of BMS-936558 versus docetaxel
- To evaluate clinical benefit in terms of ORR and OS of BMS-936558 versus docetaxel, in PD-L1 + versus PD-L1- protein expression subgroups
- To evaluate durability of and time to objective response in BMS-936558 and docetaxel groups
- To evaluate the proportion of subjects exhibiting disease-related symptom progression, as measured by LCSS, in BMS-936558 and docetaxel groups

Additional Exploratory objectives are listed in Section 1.3.3 of the protocol.

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 chemotherapy. Approximately 264 subjects will be randomized to BMS-936558 vs docetaxel in a 1:1 ratio.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment arms (see Study Design and Duration schema in Figure 1 below). Randomization will be stratified and balanced according to the following factors: prior paclitaxel vs. no paclitaxel and region (US vs Europe vs Rest of World).

Figure 1: Study Design



* ORR and PFS (by RECIST 1.1) as determined by an independent review committee (IRC)

Study Population:

Subjects must meet all eligibility criteria specified in Sections 3.3.1 and 3.3.2 of the protocol, including the following:

Key Inclusion Criteria (See Protocol Section 3.3.1 for full list of criteria)

1. Men and women ≥ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
3. 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 recurrent disease following radiation therapy or surgical resection.
4. Subjects must have experienced disease recurrence or progression during or after one prior platinum-containing doublet chemotherapy regimen for advanced or metastatic disease (see protocol Section 3.3.1 for details)
    a. Subjects who received erlotinib as maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and progressed are eligible. However, subjects who received a tyrosine kinase inhibitor after failure of a prior platinum-based therapy are excluded
    b. Subjects who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.
    c. Subjects with recurrent disease > 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum-doublet regimen given to treat the recurrence, are eligible.
5. Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization
    a. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site
6. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. 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 (See Protocol Section 3.3.2 for full list of criteria)

1. Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately 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).
2. Subjects with carcinomatous meningitis
3. Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
4. 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.
5. 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).
6. Prior treatment on the first-line study CA184104
7. Prior treatment with docetaxel
8. Subjects with a history of interstitial lung disease
9. Other active malignancy requiring concurrent intervention
10. 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
11. 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.
12. 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
13. Treatment with any investigational agent within 28 days of first administration of study treatment

Study Assessments: 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 chemotherapy. Subjects will be randomized to BMS-936558 vs Docetaxel in a 1:1 ratio.

The co-primary endpoints for the study are ORR (as assessed by the IRC) and OS. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects. BOR is defined as the best response designation, as determined by the IRC, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue BMS-936558 beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known alive date. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

Statistical Considerations:

Sample Size:

The sample size of the study accounts for the two co-primary efficacy endpoints: ORR and OS. ORR will be evaluated for treatment effect at the overall alpha of 0.01 (two-sided) with at least 90% power; no interim analysis of ORR is planned. OS will be evaluated for treatment effect at the overall alpha level of 0.04 (two-sided) with 90% power, accounting for one formal interim analysis to assess efficacy.

Approximately 264 subjects will be randomized to the two treatment arms in a 1:1 ratio. The study requires at least 189 deaths to ensure that a two-sided 4% significance level sequential test procedure with one interim analysis will have 90% power to detect a hazard ratio (HR) of 0.61, corresponding to a median OS of 7 vs. 11.4 months for the docetaxel and BMS-936558 treatment arms, respectively. Assuming a piecewise constant accrual rate (2 subjects/month during Month 0 - 1, 6 subjects/month during Month 1 - 2, 15 subjects/month during Month 2 - 4, 22 subjects/month during Month 4-6 and 30 subjects/month during Month 6 and thereafter), it will take approximately 24 months to obtain the required number of deaths for the final OS analysis (12 months for accrual and 12 months for survival follow-up). It is projected that an observed hazard ratio of 0.74 or less, corresponding to a 2.5 months or greater improvement in median OS (7 vs 9.5 months), would result in a statistically significant improvement in the final analysis of OS.

Endpoints:

ORR and OS are the co-primary endpoints for this study. The number of events and power for OS were calculated assuming an exponential distribution in each arm.

The final analysis of ORR, which requires a minimum follow-up of 6 months for all subjects, is projected to occur approximately 18 months after study initiation. This will allow sufficient follow-up for ORR to have a stable estimate. Assuming ORR on docetaxel and BMS-936558 are 10% and 35%, respectively, 264 subjects will provide more than 90% power to detect a response rate difference of 25% with an overall two-sided type I error of 0.01.

One interim analysis of OS is planned at the same time of the final analysis of ORR (18 months after study initiation), which is projected to occur after 146 deaths (77% of total deaths) have been observed based on above accrual rate and the exponential distribution in each arm. The actual interim analysis will be conducted when two conditions are fulfilled: 1) a minimum follow-up of 6 months for all subjects and 2) at least 123 deaths (65% of total deaths) have been observed. This formal comparison of OS at interim will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets α spending function with O'Brien and Fleming type of boundary in EAST v5.4. If the analysis is performed exactly at 146 deaths, the boundary for declaring superiority would be 0.016 (or 0.67 with regard to HR boundary, which corresponds to 3.4 months improvement in median OS under the assumed control arm hazard function). The boundary for declaring superiority for the final analysis after 189 events would be 0.035.

Analyses:

Efficacy Statistical Analyses:

The distribution of OS will be compared in two randomized arms via a two-sided, log-rank test stratified by prior use of paclitaxel vs. no paclitaxel use, and region. The HR and the corresponding 100x (1-adjusted α)% confidence intervals (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be

computed by Brookmeyer and Crowley method. Survival rates at 6, 12, and 18 months will also be estimated using KM estimates on the OS curve for each randomized arm.

The comparison of IRC-determined ORR will be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by above factors. An associated odds ratio and 99% CI will be calculated. Rates and their corresponding 95% exact CI will be calculated by Clopper-Pearson method for each randomized arm.

A key secondary endpoint is progression-free survival (PFS) as assessed by the IRC. It will be compared if either ORR or OS comparison is positive via a two-sided, log-rank test stratified by the same factors above. The HR and the corresponding two-sided (1-adjusted alpha)% CI will be estimated in a stratified Cox proportional hazard model using randomized arm as a single covariate. The PFS curves will be estimated using KM method. Two-sided 95% CIs for median PFS will be computed by Brookmeyer and Crowley method.

Clinical benefit will also be evaluated in subjects within PD-L1+ and PD-L1- subgroups. ORRs and corresponding 95% exact CIs using Clopper-Pearson method, 95% CIs for the difference of rates using normal approximation, OS curves using KM method, and hazard ratios with corresponding 95% CIs using Cox proportional hazards model using randomized arm as a single covariate, will be provided for subjects within PD-L1+ and PD-L1- subgroups for each randomized arm. A logistic regression model will be used to test the interaction between PD-L1 expression status (positive vs. negative) and randomized arms for the ORR endpoint. The Interaction between PD-L1 expression status and randomized arms will be tested using Cox proportional hazards model for the OS endpoint. All tests are descriptive and not adjusted for multiplicity. Other exploratory analyses, such as associations between PD-L1 status and other efficacy endpoints and evaluations of different thresholds for PD-L1 positivity, are also planned.

Other secondary endpoints include duration of objective response, time to objective response, and disease-related symptom progression rate. Statistical analyses for these endpoints are discussed in Section 8.4.

Safety Statistical Analysis:

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function and renal function will be summarized using worst grade per NCI CTCAE v4.0 criteria.

PK and Biomarker Analysis:

Serum samples will be collected to characterize pharmacokinetics of BMS-936558 and to explore exposure-safety and exposure-efficacy relationships. A variety of factors that may impact the immunomodulatory properties and efficacy of BMS-936558 will be investigated in peripheral blood, and in tumor specimens taken from all subjects prior to treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety data.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths [1]. Despite treatment with platinum- and taxane-based chemotherapy, patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of approximately 15%.[2] Unlike patients with non-squamous histology NSCLC, patients with squamous cell NSCLC have generally not benefitted from (and in fact may be negatively impacted by) several new agents, including pemetrexed and bevacizumab. [3 4] Therapeutic options for squamous cell NSCLC are particularly limited after failure of front-line chemotherapy. Therefore, while representing a minority of NSCLC cases, squamous cell NSCLC remains a disease with high burden and unmet medical need.

Immunotherapeutic approaches for the treatment of malignancy recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer.[5] Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

BMS-936558 is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby proportedly abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, BMS-936558 has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC[6]. In particular, substantial activity has been noted in the squamous histology subgroup, where objective response rates approached ~40-50%, and progression free survival approached ~6 months.[7] In general, BMS-936558 also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[8]

CA209-017 is a randomized, open-label, multinational Phase III trial of BMS-936558 monotherapy versus docetaxel in subjects with squamous cell NSCLC whose disease has

progressed during or after one prior platinum-based doublet chemotherapy regimen. The central question of the study will be to determine if BMS-936558 improves objective response rates (ORR) and overall survival (OS) over the comparator in this patient population. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of BMS-936558 in subjects with squamous cell NSCLC.

1.1 Study Rationale

1.1.1 Rationale for BMS-936558 Monotherapy

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen presenting cells.[9] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[10] [11] [12] [13] In particular, PD-L1 has been shown to be upregulated on several cancers types including NSCLC and, in some cases, correlated to negative prognosis.[14] [15] [16] [17] [18] PD-1/PD-L interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[19] Blockade of the PD-1 pathway by BMS-936558 has been studied in a variety of preclinical in vitro assays, and antitumor activity using a murine analog of BMS-936558 has been shown in a number of immunocompetent mouse cancer models.[20] Based on these and other preclinical data, PD-1 blockade by BMS-936558 has been pursued as a promising therapeutic strategy to reverse immune tolerance and enhance T-cell effector function in several tumor types including NSCLC.

Substantial monotherapy clinical activity has been observed in ≥ second line NSCLC subjects treated in the ongoing Phase 1 study of BMS-936558 (CA209003), and in particular in subjects with squamous cell NSCLC (see section 1.4.3.3). This study showed objective response rates (ORR) greater than the historical ORR for docetaxel (approximately 8-10%).[21] [22] [23] Preliminary estimates of median duration of response for NSCLC subjects in CA209003 approached 6 months, indicating response durability. Conversely, the historical median PFS for docetaxel is approximately 3 months.[21] [22] [23] Furthermore, the adverse event profile for BMS-936558 appears favorable versus docetaxel, as hematologic toxicities are currently rare and the majority of non-

hematologic toxicities are low grade and manageable. Therefore, CA209017 will test the efficacy and safety of BMS-936558 as monotherapy in previously treated squamous cell NSCLC.

1.1.2 Rationale for the use of docetaxel as a comparator

Docetaxel is one of several agents that are approved for use upon progression from first line therapy in NSCLC based improvements in PFS and OS when compared to best supportive care (BSC)[21] or active chemotherapies.[22] It has been used as a benchmark comparator vs. pemetrexed in a non-inferiority trial where PFS and OS in the docetaxel arm were 2.9 months and approximately 8 months, respectively.[23] Pemetrexed has not been approved for use in squamous cell NSCLC due to its relative lack of efficacy. Erlotinib is another agent that has been studied in second line squamous and non-squamous NSCLC; however, its uptake has not been universal in the squamous population. Docetaxel was therefore chosen as the comparator for this study, due to its clinical activity and lack of other suitable second line options in subjects with squamous cell NSCLC.

This study will stratify and balance the arms for prior paclitaxel use to make sure that the control arm is not affected by any possibility of cross-resistance. Use of docetaxel was studied in multiple trials after the use of combined agents, one had no prior paclitaxel use permitted [21], while the other had up to 42% of subjects receiving prior paclitaxel therapy.[22] The response rates and survival was equivalent. In addition, there was no reduced activity in the second-line use of docetaxel when compared with pemetrexed in the non-inferiority study despite 25% of all subjects receiving prior treatment with paclitaxel/platinum doublets.[23] The efficacy difference was not noted in other studies where docetaxel was used in combination with gemcitabine in the second-line and the majority of subjects received paclitaxel/platinum doublets in the first line. [24] [25] [26] Based on these data, subjects who received prior paclitaxel will be allowed onto the study, but will be stratified across the two treatment groups.

1.1.3 Rationale for BMS-936558 dose and schedule

The dose and schedule of BMS-936558 in this study will be 3 mg/kg every 2 weeks, based upon a February 24, 2012 analysis of safety, efficacy, and exposure-response data from the ongoing Phase 1 study CA209003. Anti-tumor activity was observed in NSCLC

subjects at dose levels of 1, 3 and 10 mg/kg every 2 weeks. Anti-tumor activity appeared to approach a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of exposure-response analyses showed that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg administered every 2 weeks. BMS-936558 was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. While the spectrum, frequency, and severity of BMS-936558-related AEs were generally similar across the dose levels tested, the 10 mg/kg dose level had numerically higher rates of Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on these observations, a dose of 3 mg/kg every 2 weeks was chosen for further study. Further information on observed safety, efficacy and pharmacokinetic data from CA209003 is reviewed in Section 1.4.3.

1.1.4 Rationale for Initial Tumor Assessment at 9 weeks

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in the Phase 1 CA209003 study of BMS-936558. Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size appearing as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Another hypothesis is that the kinetics of tumor growth may initially outpace anti-tumor immune activity in some individuals. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. For these reasons, the initial tumor assessment in CA209003 was conducted at 8 weeks, and it is unknown if an earlier assessment would demonstrate similar activity due to premature termination of study treatment.

To mitigate the risk of detecting false-progression early in the course of treatment with BMS-936558, the initial tumor assessment for both arms in this study will take place at Week 9 (± 5 days). Thereafter, all subsequent tumor assessments will take place regularly every 6 weeks (± 5 days) until documented disease progression or treatment discontinuation, whichever occurs later. This will maintain blinding of the IRC by synchronizing the assessment schedule for all subjects.

1.1.5 Rationale for collection of tumor tissue and evaluation of tumor PD-L1 expression as a potential predictive biomarker

Aberrant expression of PD-L1 protein by tumor cells (retrospectively detected by IHC) has been reported in a number of human malignancies, especially in relation to poor prognosis, in multiple tumor types including squamous and non-squamous NSCLC .[14 15 16 17 18 27 28 29] In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells is related to tumor aggressiveness [16 30] and subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from cancer than subjects exhibiting low levels of PD-L1 expression. These findings may be explained by the notion that high PD-L1 expression leads to immune evasion. This hypothesis is supported by separate studies demonstrating that PD-L1 expressed by tumor cells enhances apoptosis of activated tumor-specific T cells in vitro and that the expression of PD-L1 protects tumor cells from the induction of apoptosis by effector T cells. In NSCLC, blocking PD-L1 allows for the increase of tumor-infiltrating CD8+ T cells and an increased production of IFN-γ but no difference noted in peripheral blood CD8+ T cells when subjects with NSCLC were compared with healthy controls.[31] These high levels of PD-L1 protein expression in NSCLC are also associated with poor prognosis and the presence of tumor infiltration by immature dendritic cells.[32]

Preliminary data indicate PD-L1 protein expression in tumors may correlate with BMS-936558 clinical activity. Sixty-one pretreatment tumor specimens from a limited subset (N=42) of subjects in CA209003 (18 melanoma, 10 non-small-cell lung, 7 colorectal, 5 renal-cell, and 2 prostate cancer) were analyzed for tumor cell surface PD-L1 expression. Biopsy specimens from 25 of 42 subjects were positive for PD-L1 expression by IHC. Among these subjects, 9 (36%) achieved an OR. Among 17 subjects with PD-L1-negative tumors, none achieved an OR. This analysis is based on optional biopsies from a non-random subset of the population, and testing of a statistical hypothesis was not pre-specified. These preliminary results must, therefore, be interpreted with caution. Importantly, only 10/42 subjects in this subset had NSCLC, with only one responder in the PD-L1+ group. Therefore, these data are not conclusive as to the positive or negative predictive value of PD-L1 expression in NSCLC, and further analyses of a larger number of samples from CA209003 are planned.

In order to more thoroughly assess the role of PD-L1 protein expression as a predictive biomarker, archival or recent tumor tissue will be collected prospectively from all randomized subjects in this study, and a retrospective analysis of efficacy by PD-L1 expression status will be conducted. Due to the preliminary nature of the Phase 1 data and current lack of a verified IHC assay, subjects enrolled to CA209017 will not be selected or stratified by PD-L1 expression status. However, based on preliminary PD-L1 prevalence estimates in NSCLC of approximately 45-70% [17](and unpublished data), a reasonable number of PD-L1 positive subjects are anticipated to accrue to each treatment arm for the analysis. Additionally, the sponsor is in the process of developing a verified IHC assay that can be used to reproducibly measure PD-L1 expression in tumor tissue. Contingent on development of an optimized assay, future prospective analyses of PD-L1 expression and clinical outcome are planned.

1.1.6 Rationale for Patient Reported Outcomes Evaluation

Due to the proposed increase in ORR, OS, and PFS from treatment with BMS-936558 relative to docetaxel, it is hypothesized that time to significant disease-related symptoms, as measured by the Lung Cancer Symptom Scale (LCSS) will also increase related to BMS-936558 over docetaxel. The EQ-5D will be used to assess general health status and the data will be used to calculate utilities for use in economic models.

1.2 Research Hypothesis

BMS-936558 improves ORR and/or increases OS as compared with docetaxel, in squamous cell NSCLC subjects treated with prior platinum-based doublet chemotherapy.

1.3 Objectives

1.3.1 Primary Objective

To compare the ORR and OS of BMS-936558 versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy

1.3.2 Secondary Objectives

- To compare the progression-free survival (PFS) of BMS-936558 versus docetaxel
- To evaluate clinical benefit in terms of ORR and OS of BMS-936558 versus docetaxel, in PD-L1+ versus PD-L1- protein expression subgroups

- To evaluate durability of and time to objective response in BMS-936558 and docetaxel groups
- To evaluate the proportion of subjects exhibiting disease-related symptom progression, as measured by LCSS, in BMS-936558 and docetaxel groups

1.3.3 Exploratory Objectives

- To assess the overall safety and tolerability of BMS-936558 versus docetaxel
- To explore potential predictive biomarkers of BMS-936558 efficacy (such as ORR, PFS and OS) in peripheral blood and tumor specimens, including antibodies to tumor antigens and proteins involved in regulating immune responses (eg PD-1, PD-L1, PD-L2)
- To assess the effects natural variation single nucleotide polymorphism (SNPs) in select genes (eg PD-1, PD-L1, PD-L2, CTLA-4) has on clinical endpoints and/or on the occurrence of adverse events
- To characterize pharmacokinetics of BMS-936558 and explore exposure-response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints
- To characterize immunogenicity of BMS-936558
- To assess the subject's overall health status using the EQ-5D Index and visual analog scale.

1.4 Product Development Background

BMS-936558 is in clinical development for the treatment of subjects with NSCLC, renal cell carcinoma (RCC) and melanoma. The initial registrational opportunity for BMS-936558 in NSCLC is focused on monotherapy in the second-line setting, after a subject has received a platinum-based combination. This will be evaluated through two studies, CA209017 in a squamous population and CA209057 in a non-squamous population. In CA209017, ORR and OS of BMS-936558 will be evaluated as compared with docetaxel in subjects with squamous histology NSCLC. Other studies to be conducted in the NSCLC program will assess the efficacy of BMS-936558 in additional lines of therapy, as monotherapy and/or in various combinations.

1.4.1 Mechanism of Action of BMS-936558

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[33] [34] [35] Support for the role of immunosurveillance in NSCLC is suggested in retrospective analyses demonstrating a correlation between tumor infiltrating lymphocytes in surgically resected specimens and recurrence free survival.[36] [37] [38] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[39] Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA[29]. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon -γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes [40]. These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, BMS-936558 binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ~ 1 nM). BMS-936558 binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by BMS-936558 results in a reproducible enhancement of both proliferation and IFN-γ release in the

mixed lymphocyte reaction (MLR). Using a CMV-re-stimulation assay with human PBMC, the effect of BMS-936558 on antigen specific recall response indicates that BMS-936558 augmented IFN-γ 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 BMS-936558 enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[20]

1.4.2 Non-small cell lung cancer (NSCLC) - Background and Treatments

Lung cancer is the leading cause of cancer-related deaths globally. An estimated 221,130 new cases of lung cancer will be diagnosed in 2011.[2] The majority of subjects (approximately 78%) are diagnosed with advanced or metastatic disease. Progression after first-line therapy occurred in nearly all of these subjects and the 5 year survival rate is only 3.6% in the refractory setting. [2] There is a particular unmet need among patients who have squamous cell NSCLC (representing up to 25% of all NSCLC) as there are few treatment options after first-line therapy (ie, pemetrexed is not a treatment option and erlotinib was not separately evaluated in a squamous cell subset of patients). [3] [24] In addition, there are several targeted therapeutics that are restricted to the non-squamous population due to adverse events (ie, bevacizumab which caused fatal hemorrhage in squamous cell subjects).[4] According to NCCN guidelines, the use of single agent chemotherapy is standard-of-care for patients with recurrent and metastatic NSCLC after failure of platinum-based therapy.[2] Historical median PFS rates in second-line NSCLC are approximately 2.6 - 3.2 months, and median OS rates approximately 6.7 to 8.3 months (longer in the recent ZODIAC trial, 10+ months). [22] [23] [24] [55] [41] Current therapy in second-line includes docetaxel, erlotinib and pemetrexed (only in non-squamous histologies).[22] [23] [24] No agent has shown superiority in OS when compared to docetaxel. Different docetaxel schedules (other than the standard q3 weeks), chemotherapy doublets using docetaxel, and other comparative agents have not shown improvement over docetaxel in this line of therapy. [42] [43] [44] [45] [56]

1.4.2.1 Squamous cell NSCLC

Among the different histologies of NSCLC, squamous histology typically represents 25% of all lung cancer cases.[46] Most studies involving first-line and second-line therapy did not specifically separate subjects by histology, although this was recorded in all of the pivotal trials. [3 22 23 24] The first study that showed a difference in histology involved the comparison of gemcitabine and cisplatin to pemetrexed and cisplatin. In this study, subjects with squamous cell NSCLC had a median survival time of 10.8 months with the gemcitabine combination while it was only 9.4 months with pemetrexed. This is compared with the median survival time of 10.9 months with gemcitabine versus 12.6 months with pemetrexed in adenocarcinoma and 6.7 months with gemcitabine versus 10.4 months with pemetrexed in large cell lung cancer.[3] A subanalysis of the pemetrexed non-inferiority study in second-line therapy[23] showed a statistically significant improvement in the combined non-squamous histologies when compared with docetaxel (9.3 months vs. 8.0 months (HR 0.778)) but not in squamous (6.2 months vs. 7.4 months (HR 1.563))[47]. Additional data has shown that there is a poorer prognosis among subjects with squamous cell NSCLC due to comorbidities related to smoking history, larger tumors with lymphatic and vascular invasion, and the presence of more poorly differentiated tumors although the risk of disease recurrence after initial treatment is the same between adenocarcinoma and squamous cell.[48]

The treatment of NSCLC has also been defined by the development of understanding of somatic mutations that drive tumor growth and development. For example, significant clinical benefit was noted among subjects with EGFR mutations when treated with EGFR TKIs [49 50]. However, low responses were noted among male smokers with squamous cell lung cancer when they were treated with erlotinib as compared with subjects who were female, nonsmokers and with adenocarcinoma.[51] It has been noted that EGFR mutations were observed in only 2.7% of squamous cell samples [52] and EGFR testing is not recommended in the NCCN guidelines.[2] Recently, analysis of genetic changes in squamous cell lung cancer has shown multiple potential targets for new drugs but this remains immature.[53]

Currently, second-line treatment for squamous cell lung cancer remains an area of unmet need. Docetaxel remains the benchmark treatment [2] in this line of therapy although erlotinib may also used with less frequency.

1.4.2.2 Docetaxel (Taxotere®)

Docetaxel is a cytotoxic microtubule inhibiting antineoplastic agent in the taxane class that is indicated as single agent treatment for locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel is recommended to be administered in a facility equipped to manage possible complications such as anaphylaxis. The dosing is recommended at 75 mg/m² administered intravenouosly over one hour on an every 3 week schedule. Per the Taxotere® label, the premedication regimen should be oral corticosteroids such as dexamethasone at a dose of 8 mg BID for 3 days starting one day prior to administration and continued for one day after infusion[54].

1.4.2.3 Safety of docetaxel

The major adverse events related to docetaxel are primarily hematologic. The key grade 3 to 4 hematologic toxicities include neutropenia (30 - 67%), anemia (2 - 5%) and thrombocytopenia (< 1 - 2%). Non-hematologic adverse events related to docetaxel include febrile neutropenia (4.7 - 12.7%), asthenia (47 - 55%), alopecia (35%), nausea (26 - 36%), diarrhea (12-36%), peripheral neuropathy (15 - 24%), vomiting (17%), and fluid retention (5 - 16%). [21] [22] [23] [55] [56] [54] Warnings related to docetaxel include treatment-related mortality increases with abnormal liver function at higher doses, should not be given to subjects if the total bilirubin is greater than institutional upper limit of normal (ULN), or if AST and/or ALT is greater than 1.5X ULN concomitant with alkaline phosphatase greater than 2.5X ULN, should not be given if the neutrophil count of the subject is less than 1500 cell/mm³, should not be given if subjects have a history of severe hypersensitivity to docetaxel or drugs formulated with polysorbate 80, and may cause severe fluid retention.[54]

1.4.3 BMS-936558 Clinical Results

Two studies contributed to most of the clinical experience with BMS-936558 in subjects with malignancies. CA209001 was a Phase 1 single-dose dose escalation study in subjects (N = 39) with previously treated advanced or metastatic cancer. Subjects

received a single dose of BMS-936558 at 0.3, 1, 3, or 10mg/kg with an option for re-treatment at 3 months. CA209003 is an ongoing Phase 1 open-label, multiple dose escalation study in subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC (squamous and non-squamous), colorectal cancer, and hormone-refractory prostate cancer. Subjects received BMS-936558 at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of February 24, 2012, 296 subjects were evaluable for safety (cutoff date February 24, 2012) across the entire dose range, including 122 NSCLC subjects, and 236 were evaluable for efficacy (cutoff date July 1, 2011), including 76 subjects with NSCLC.

1.4.3.1 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of BMS-936558 was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~350 subjects from CA209001, CA209002, and CA209003.

Single dose PK of BMS-936558 was evaluated in 39 subjects with mutiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of BMS-936558 is linear in the range of 0.3 to 10 mg/kg with dose- proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (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-HALF of BMS-936558 is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of BMS-936558 may be similar to IgG4. Both elimination and distribution of BMS-936558 appear to be independent of dose in the dose range studied. Additional details are provided in investigator brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from CA209001, CA209002 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of BMS-936558.

1.4.3.2 Safety Summary

In CA209001, treatment-related AEs were reported for 35 of 39 (89.7%) subjects; 12 subjects (30.8%) had reported treatment-related AEs of Grade 3 or 4. The most frequently reported AEs, regardless of causality, included fatigue (56.4%), nausea (43.6%), proteinuria (38.5%), constipation (33.3%), back pain (33.3%), dry mouth (28.2%), vomiting (28.2%), rash (25.6%) and dyspnea (25.6%). Additional events of interest included diarrhea (8 subjects) and thyroid stimulating hormone increased (7 subjects); none were serious or of high grade. Two subjects reported treatment-related SAEs of hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). There was no dose-related pattern with regard to the incidence, severity, or relationship of AEs. Common laboratory abnormalities (reported in ≥ 10% of subjects) that were considered related to BMS-936558 included decreases in CD4 counts, lymphopenia, and increases in C-reactive protein. A Grade 4 event of lymphocyte count decreased was reported for 1 subject. Twelve (12) deaths were reported during the course of the study or within 30 days of last dose of study drug, all considered unrelated to BMS-936558.

No MTD was identified in CA209003 at any dose level. BMS-936558 related AEs of any grade occurred in 70% of subjects. The most frequent drug-related AEs occurring in ≥ 5% of subjects included fatigue (24%), rash (12%), diarrhea (11%), pruritus (10%), nausea (8%), decreased appetite (8%), hemoglobin decreased (6%) and pyrexia (5%). The majority of events were low grade, with grade 3-4 drug-related AEs observed in 14% of subjects. The most common Grade 3-4 drug-related AEs occurring in ≥ 1% of subjects were fatigue (2%), pneumonitis (1%), hypoxia (1%), diarrhea (1%), colitis (1%), abdominal pain (1%), AST/ALT increased (1% each), blood alkaline phosphatase increased (1%), lipase increased (1%), pneumonia (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 11% of subjects. Grade 3-4 drug-related SAEs occurring in ≥ 1% of subjects were: pneumonitis (1%), pneumonia (1%), lipase increased (1%) and diarrhea (1%). The spectrum, frequency, and severity of BMS-936558-related AEs were generally similar across dose levels and histological subtypes.

Drug-related adverse events of special interest (AEOSIs), with potential immune-related etiologies, included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis, among others. Hepatic or gastrointestinal AEOSIs were managed with treatment

interruption and administration of corticosteroids, and were generally completely reversible. Endocrine AEOSIs were managed with replacement therapy. Several subjects in these categories successfully reinitiated treatment with BMS-936558. Drug-related pneumonitis occurred in 3% of subjects; grade 3-4 pneumonitis developed in 3 subjects (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In 3 subjects, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were 3 (1%) drug-related deaths, due to pneumonitis.

Because of the potential for the development of BMS-936558-related AEs including AEOSI, management algorithms have been developed for suspected pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, and endocrinopathy, and are contained within the IB. Additional details on the safety profile of BMS-936558, including results from other clinical studies, are also available in the IB.

1.4.3.3 Anti-tumor Activity Summary

Efficacy data from CA209003 was evaluated as of July 1, 2011, which provided a minimum follow-up of 8 months. Clinical antitumor activity was observed in melanoma, RCC, and NSCLC at all BMS-936558 doses tested. NSCLC subjects were treated at doses of 1, 3, and 10 mg/kg. Antitumor activity was mainly observed in the 3 and 10 mg/kg dose groups, and exposure-response appeared to be relatively flat at doses ≥ 3 mg/kg. At the 3 and 10 mg/kg dose levels, the RECIST-defined objective response rates for all histologies were 32% and 18%, respectively. The corresponding disease control rates (which included any subject who achieved a best overall response of CR, PR or SD) were 53% and 46%, respectively. PFS rates at 24 weeks were 41%, and 24%, respectively, indicating durable disease control. Differential activity was observed between squamous versus non-squamous histologies. Substantial activity was noted in the squamous histology subgroup (n=18), where the ORR and DCR in the 3 mg/kg dose group were 50% and 67%, respectively (the ORR for squamous histology subjects across all dose groups was 33%). Responses were durable; as of the cutoff date, the median PFS in the 3mg/kg squamous group had not been reached, and 3 of 6 subjects had experienced PFS > 6 months. One subject who achieved PR (67% tumor reduction) experienced a response duration of 134 weeks. Activity in NSCLC is especially notable in that the majority of subjects had received 2 or more prior therapies. These preliminary data

suggest that BMS-936558 induces substantial durable disease control in heavily pretreated subjects with NSCLC, and in particular in subjects with squamous histology.

1.5 Overall Risk/Benefit Assessment

Subjects with metastatic squamous cell NSCLC who progress with first-line therapy represent a great unmet need. The clinical activity of BMS-936558 observed to date in squamous cell NSCLC suggests the potential for improved clinical outcomes as monotherapy. However, the potential benefit over standard of care docetaxel is not yet known. Docetaxel has a well characterized adverse event profile consistent with cytotoxic chemotherapy, including the potential for serious pancytopenia, fluid retention, peripheral neuropathies, asthenia, diarrhea, nausea and vomiting. BMS-936558 also has the potential for clinically relevant adverse events including liver toxicities, thyroiditis, pneumonitis, and diarrhea. However, the activity and manageable AEs profile observed with BMS-936558 supports a head-to-head evaluation versus docetaxel in second-line squamous cell NSCLC.

To assure an ongoing favorable benefit-risk assessment for subjects enrolled onto CA209017, an independent Data Monitoring Committee (DMC) will be utilized to monitor the activity and safety of BMS-936558 versus docetaxel throughout the conduct of the trial.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the

protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3) Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6) Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke subjects, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion

and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

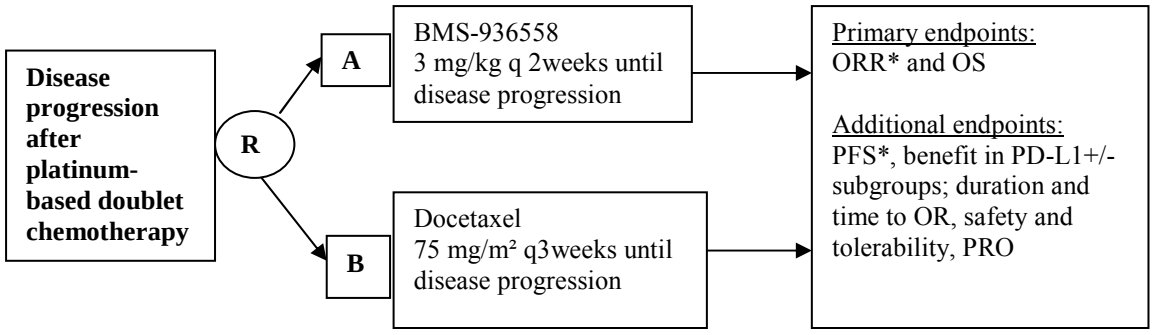
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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 chemotherapy. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment arms in a 1:1 ratio (see Study Design and Duration in Figure 3.1 below). Randomization will be stratified according to the following factors: prior treatment with paclitaxel-based doublet vs. other doublet, and region (US vs. Europe vs. Rest of World).

Figure 3.1: Study Design



* ORR and PFS (by RECIST 1.1) as determined by an independent review committee (IRC)

Treatment should be initiated within 3 days of randomization. BMS-936558 or docetaxel (depending on randomized treatment Arm) will be administered as an IV infusion over 60 minutes on Treatment Day 1. A treatment cycle is defined as 2 weeks for BMS-936558 and 3 weeks for docetaxel.

This study will consist of 3 phases: screening, treatment, and follow-up.

Screening:

- Begins by establishing subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID.
- Tumor tissue (archival or recent tumor biopsy) must be available and received by the central lab for correlative studies in order for a subject to be randomized. Subjects must consent to allow the acquisition of tumor tissue by study personnel for performance of the correlative studies. (Table 5.1A)
- Baseline disease or tumor assessments should be performed within 28 days of randomization (according to Table 5.1A).
- Subject is assessed for study eligibility within the required timeframe found in Table 5.1A.

Treatment:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to one of the treatment arms. Treatment should begin within 3 days of randomization.
- All of the laboratories and vital signs will be collected on Day 1 of each cycle, and specific laboratories will be performed more frequently during the first cycle. (according to Table 5.1B or Table 5.1C, depending on the randomized treatment arm) Adverse event assessments should be documented at each clinic visit.
- Biomarker, PK and immunogenicity samples will be done according to the schedules in Section 5.1 (Tables 5.1B, 5.1C, 5.1D, and 5.1E).
- Patient-reported outcome (PRO) instruments will be completed after randomization, prior to the first dose of study therapy on Day 1, and prior to study procedures and dosing on Day 1 of each visit for which an ePRO instrument assessment is scheduled, according to Table 5.1B or Table 5.1C, depending on randomized treatment assignment.
- Study drug is administered as an IV infusion on Treatment Day 1 of each cycle (frequency is dependent on the treatment arm) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.
- Subjects will be evaluated for response according to the RECIST 1.1 criteria. Radiographic assessments will be obtained in both treatment arms at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 beyond

progression), lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.

- Baseline and all subsequent scans will be submitted to an independent review committee (IRC), once the subject is randomized and throughout the study period.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 for a complete list of reasons for discontinuation.

Follow-up:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will have two follow-up visits for safety within the first 100 days from the last dose of study therapy, according to Section 5.3.3 and Table 5.1D. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.
- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 5 days) until disease progression, lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.
- All subjects will be followed for overall survival every 3 months until death, lost to follow-up, or withdrawal of study consent.
- For subjects randomized to receive BMS-936558 (Arm A) only, the 2 follow-up visits will include PK and immunogenicity samples according to Table 5.1E.
- ePRO instruments will be completed at a frequency according to Table 5.1D (first two follow-up visits).

This study will end when analysis of survival is complete. The duration of study will be approximately 2 years (24 months).

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of the sponsor. The sponsor

reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests including completion of patient reported outcomes questionnaires and other requirements of the study.

2) Target Population

a) Men and women ≥ 18 years of age

b) 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 recurrent disease following radiation therapy or surgical resection.

c) Subjects must have experienced disease recurrence or progression during or after one prior platinum-containing doublet chemotherapy regimen for advanced or metastatic disease.

i) Subjects who received erlotinib as maintenance therapy (non-progressors with platinum-based doublet chemotherapy) and progressed are eligible. However, subjects who received a tyrosine kinase inhibitor after failure of a prior platinum-based therapy are excluded.

ii) Subjects who received adjuvant or neoadjuvant platinum-doublet chemotherapy (after surgery and/or radiation therapy) and developed recurrent or metastatic disease within 6 months of completing therapy are eligible.

iii) Subjects with recurrent disease > 6 months after adjuvant or neoadjuvant platinum-based chemotherapy, who also subsequently progressed during or after a platinum- doublet regimen given to treat the recurrence, are eligible.

d) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization
   i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site

e) Eastern Cooperative Oncology Arm (ECOG) performance status of ≤ 1

f) A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.

g) All baseline laboratory requirements will be assessed and should be obtained within **-14** days of randomization. Screening laboratory values must meet the following criteria
   i) WBCs ≥ 2000/μL
   ii) Neutrophils ≥ 1500/μL
   iii) Platelets ≥ 100 x 10^3/μL
   iv) Hemoglobin ≥ 9.0 g/dL
   v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

   vi) AST ≤ 1.5X ULN
   vii) ALT ≤ 1.5X ULN
   viii) Total bilirubin ≤ ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL)

h) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization

3) Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 2. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than

1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator.

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

c) Women must not be breastfeeding

d) Men who are sexually active with WOCBP 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. Men that are sexually active with WOCBP must follow instructions for birth control for a period of 90 days plus the time required for the investigational drug to undergo five half lives.

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately 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).

b) Subjects with carcinomatous meningitis

2) Medical History and Concurrent Diseases

a) Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

b) 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.

c) 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).

d) Prior treatment on the first-line study CA184104

e) Prior treatment with docetaxel

f) Subjects with a history of interstitial lung disease

g) Other active malignancy requiring concurrent intervention

h) 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

i) 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.

j) 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

3) Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection.

4) Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of severe hypersensitivity reaction to prior paclitaxel

c) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.

5) Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6) Prohibited Treatments and/or Restricted Therapies

a) Ongoing or planned administration of anti-cancer therapies other than those specified in this study

b) Use of corticosteroids or other immunosuppressive medications as per Exclusion Criteria 2b

c) Strong CYP3A4 inhibitors (See Section 3.4.1)

d) Treatment with any investigational agent within 28 days of first administration of study treatment

7) Other Exclusion Criteria

a) 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

b) Prisoners or subjects who are involuntarily incarcerated

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products
- Other parenteral products may require washout periods as long as 6 months

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following strong CYP3A4 inhibitors should be avoided during the study. This includes (but is not limited to):

- Ketoconazole
- Itraconazole

- Clarithromycin
- Atazanvir
- Indinavir
- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

The following medications are prohibited during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in this Section 3.4.3).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

Palliative and supportive care for disease related symptoms (including local radiotherapy, bisphosphonates and RANK-L inhibitors) may be offered to all subjects prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomization per Inclusion criteria 2h).

3.4.2 Other Restrictions and Precautions

Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, 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.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids (eg, prednisone ≤ 10 mg/day) are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

The potential for overlapping toxicities with radiotherapy and BMS-936658 currently is not known. Therefore, palliative radiotherapy is not recommended while receiving BMS-936558. If palliative radiotherapy is required, then BMS-936558 should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to Grade ≤ 1 prior to resuming BMS-936558. Only non-target bone lesions that do not include lung tissue in the planned radiation field may receive palliative radiotherapy. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. If warranted, symptoms requiring palliative radiotherapy should be evaluated for objective evidence of disease progression.

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)

- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specific reasons for discontinuation (See Section 4.3.5**)**

All subjects who discontinue should comply with protocol specified follow-up and survival procedures as outlined in Section 5. The ONLY exception to this requirement is when a **subject withdraws consent** for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

4 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g. backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

4.1 Study Treatments

BMS-936558 100 mg (10 mg/mL) will be packaged in an open-label fashion.

Ten BMS-936558, 10 mL vials will be packaged within a carton (see Table 4.1), and are not subject or treatment arm specific. Vial assignments by subject will be made through the IVRS to track usage and resupply.

Subjects will be randomized to one of 2 treatment arms on study: BMS-936558 at 3mg/kg, or docetaxel at 75mg/m^2. Treatment should be initiated within 3 days of randomization. Each subject will be dosed at a frequency according to their treatment Arm assignment until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.

Table 4.1: Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558 Solution for Injection	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 to 8 °C. Protect from light and freezing.
Docetaxel Concentrate for solution for infusion	160 mg (20 mg/mL)[a]	8 mL vial/ Open-label	1 vial per carton / Open-label	Pale yellow to brownish yellow solution	Do not store above 25°C. Store in original package and Protect from light.
Dexamethasone Tablets	4 mg [a]	Wallet (blister) card of 20 tablets / Open-label	N/A	Scored tablets	Store at 15-25° C.

* Dexamethasone is being provided by Bristol-Myers Squibb for the docetaxel arm (required premedication).

** Medications used to treat BMS-936558-related infusion reactions are (eg diphenhydramine, acetaminophen/paracetamol, corticosterioids) considered NIMPs (noninvestigational products) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert or summary of product characteristics (SmPC). For further details related to these medications and BMS-936558-related infusion reactions, please see section 4.3.6.

[a] For sites/countries in which investigative site staff will procure locally marketed product, the potency/packaging size may differ based on the locally available product.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- BMS-936558
- Docetaxel

Docetaxel will be provided by BMS as listed in Table 4.1 for certain countries and may be procured by the investigative sites in other countries as local commercial product, where allowed by local regulations. The sites will also procure IV bags, diluents, and micron in-line filters (ie 0.2/ 0.22 micron; see current BMS-936558 Investigator Brochure for required filter details).

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational products are:

Dexamethasone (for 3 days in the docetaxel arm only as premedication), and any medications used to treat BMS-936558 related infusion reactions (see section 4.3.6).

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately. BMS-936558 vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Docetaxel and dexamethasone should be stored according to the market product package insert or clinical label.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (e.g. required diluents, administration sets).

Recommended safety measures for preparation and handling of BMS-936558 include laboratory coats and gloves.

After BMS-936558 has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current BMS-936558 Investigator Brochure. [20]

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936558 and polyolefin bags have been observed.

BMS-936558 is to be administered as a 60 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) and administration will be found in the current Investigator brochure for BMS-936558.[20]

For sites utilizing the docetaxel 160 mg vials provided by Bristol-Myers Squibb, the preparation instructions found within the current SmPC should be followed. [57]

For sites utilizing locally-sourced docetaxel, please follow storage and administration instructions on the package insert or SmPC. [54] [57]

4.2 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth

Once enrolled in IVRS, enrolled subjects that have signed informed consent and met all eligibility criteria will be ready to be randomized through the IVRS, upon confirmation of receipt of required tissue sample by the central lab. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Diagnosis
- Date of informed consent
- Prior paclitaxel vs. other prior treatment
- Region (US/ Canada vs Europe vs Rest of World)

Subjects meeting all eligibility criteria and randomized onto the study will be assigned to one of the two treatment arms, and stratified by the following factors: prior paclitaxel vs. other prior treatment, and region. The randomization will be carried out via permuted blocks within each stratum.

4.2.1 Treatment Arms

Arm A: BMS-936558

No premedications are recommended for initiation of dosing.

Arm B: Docetaxel

Dexamethasone 8mg PO BID (or institutional equivalent) on the day before, day of, and day after chemotherapy. Please use the institutional standard for dexamethasone dosing.

4.3 Selection and Timing of Dose for Each Subject

Subjects randomized to Arm A (the experimental arm) will receive treatment with BMS-936558 as a 60 minute IV infusion, on Day 1 of a treatment cycle every 2 weeks. Dosing calculations should be based on the body weight assessed at the start of each cycle as per Table 5.1B. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of BMS-936558 allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for BMS-936558 on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.6.

Subjects randomized to Arm B (the control arm) will receive treatment with docetaxel as a 60 minute IV infusion on Day 1 of a treatment cycle every 3 weeks. Dosing calculations should be based upon the body surface area calculation assessed as per Table 5.1C. The dose should remain the same if the subject's weight is within 10% of the baseline weight and/or prior dose weight. Dose modifications for toxicity will be performed according to Section 4.3.2.2. Subjects may be dosed no less than 19 days from the previous dose.

On both arms, treatment may be delayed for up to a maximum of 6 weeks from the last dose (See Sections 4.3.1 and 4.3.5).

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria.

In some cases, the natural history of immunotherapy-related AEs of special interest can differ and be more severe than AEs caused by other therapeutic classes. Early recognition

and management may mitigate severe toxicity. Evaluation and Management Guidelines were developed to assist investigators and can be found in the Investigator Brochure:

- Suspected Pulmonary Toxicity
- Diarrhea and Colitis
- Suspected Hepatotoxicity (including asymptomatic LFT elevations)
- Suspected Endocrinopathy

4.3.1 Dose Delay Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

4.3.1.1 BMS-936558 Dose Delay Criteria

BMS-936558 administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose delay
  - If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.1.2 Docetaxel Dose Delay Criteria

Docetaxel administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay

- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, neutrophil count, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay
  - Should not be given if neutrophil counts are < 1500 cells/mm^3
  - Should not be given if total bilirubin > upper limit of normal (ULN), or if AST and/or ALT > 1.5xULN concomitant with alkaline phosphatase > 2.5xULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Subsequent dose reductions may be required as per Section 4.3.2.2.

Subjects receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

4.3.2 Dose Reductions

4.3.2.1 BMS-936558 Dose Reductions

There will be no dose modifications of BMS-936558.

4.3.2.2 Docetaxel Dose Reductions

Dose reductions of docetaxel may be required, and will be performed according to Table 4.3.2.2.

Table 4.3.2.2: Dose Reductions of Docetaxel [54]

Dose Level	Docetaxel
Starting dose	75 mg/m^2
First dose reduction	55 mg/m^2
Second dose reduction	37.5 mg/m^2
Third dose reduction	Discontinue docetaxel

Doses of docetaxel will be modified for subjects who experience febrile neutropenia, neutrophils < 500 cell/mm³ for more than one week despite growth factor support, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities

during docetaxel treatment. Subjects should have treatment delayed according to Sections 4.3.1.2 and 4.3.3.2, and then resumed at one dose level reduction (55 mg/m²). Should these AEs occur after the first dose reduction, then a second dose reduction to 37.5 mg/m² is permitted. If a third dose reduction is required, then the subject should discontinue docetaxel treatment and enter the follow-up phase.

Subjects who develop Grade ≥ 3 peripheral neuropathy, or who otherwise meet criteria specified in Section 4.3.5.2, should discontinue docetaxel treatment and enter the follow-up phase.

4.3.3 Criteria to Resume Dosing

4.3.3.1 Criteria to Resume Treatment with BMS-936558

Subjects may resume treatment with BMS-936558 when the drug-related AE(s) resolve(s) 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, or colitis 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, except as specified in Section 4.3.5.1.

4.3.3.2 Criteria to Resume Treatment with Docetaxel

Subjects may resume treatment with docetaxel when the drug-related AE(s) resolve(s) 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 decreased neutrophil counts, or with elevations in total bilirubin, AST or ALT must meet criteria for resuming treatment according to the boxed warning contained within the docetaxel Prescribing Information
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5.2) should have treatment permanently discontinued

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in section 4.3.5.2.

When resuming docetaxel treatment, please follow the dose reduction recommendations noted in Section 4.3.2.2.

4.3.4 Treatment Beyond Disease Progression

As described in Section 1.4.3.3., accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[58]

Subjects treated with docetaxel (Arm B) will not be permitted to continue their treatment beyond initial RECIST 1.1 defined PD.

Subjects treated with BMS-936558 (Arm A) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Continue to meet all other study protocol eligibility criteria
3. Tolerance of study drug
4. Stable performance status
5. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
6. Subject provides written informed consent prior to receiving additional BMS-936558 treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the BMS medical Monitor and documented in the study records.

A radiographic assessment/ scan should be performed within six (6) weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with BMS-936558.

If the investigator feels that the BMS-936558 subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on Table 5.1B. The decision to continue treatment should be discussed with the BMS Medical Monitor and documented in the study records.

For the subjects who continue BMS-936558 study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

For subjects in both treatment arms, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as ‘symptomatic deterioration’. Every effort should be made to document objective progression (ie radiographic confirmation) even after discontinuation of treatment.

4.3.5 Treatment Discontinuation Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is discontinued.

4.3.5.1 BMS-936558 Dose Discontinuation

BMS-936558 treatment should be permanently discontinued for the following:

- Any Grade ≥ 2 drug-related uveitis, 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 for laboratory abnormalities, drug-related bronchospasm, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related 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 BMS-936558 dosing

4.3.5.2 Docetaxel Dose Discontinuation

Docetaxel treatment should be permanently discontinued for the following:

- Any Grade ≥ 3 peripheral neuropathy
- Any Grade 3 non-skin drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - ♦ Grade 3 drug-related thrombocytopenia 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 > 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 docetaxel dosing

4.3.6 Treatment of BMS-936558-Related Infusion Reactions

Since BMS-936558 contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated).

- 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 BMS-936558 administrations.

For 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).

- Stop the BMS-936558 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 BMS-936558 will be administered at that visit.

- 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 BMS-936558 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).

- Immediately discontinue infusion of BMS-936558. 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. BMS-936558 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.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.4 Blinding/Unblinding

Not applicable.

An open-label (rather than blinded) study design was selected because the management of similar AEs will differ between treatment arms, given the different mechanisms of action of docetaxel and BMS-936558. Different dose modification rules (no dose reductions for BMS 936558 vs allowance for dose reductions for docetaxel) and different drug-drug interaction profiles add complexity to any blinding strategy.

Subjects have potentially different AEs, as BMS-936558 has shown immune-related events while docetaxel has an adverse event profile that consists primarily of hematologic events. Although both drugs have been noted to cause pulmonary AEs, these events are treated differently. With docetaxel, pulmonary AEs are mainly due to neutropenic fever and pneumonia, requiring broad-spectrum antibiotics and growth factors. With BMS-936558, pulmonary AEs are immune related and are treated with systemic steroids. If this trial is blinded, the management of AEs would potentially be delayed or detrimental to the subject.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g. cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the

containers. The method of disposal, i.e. incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.

- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.7 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1A: Screening Assessments and Procedures (CA209017) For ARMS A and B

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to randomization
Medical History	X	
Safety Assessments		
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) Obtain vital signs at screening visit and within 72 hours of first dose
Physical Measurements (including Performance Status)	X	Includes Height and Weight, and ECOG status
Laboratory Tests	X	Labs performed locally within 14 days prior to randomization: CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4, HBV sAg, HCV RNA
Pregnancy Test	X	Performed within **24** hours of randomization (serum or urine for WOCBP only)

Table 5.1A: Screening Assessments and Procedures (CA209017) For ARMS A and B		
Procedure	**Screening Visit**	**Notes**
Assessment (of signs and symptoms)	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of study randomization, prior to study treatment initiation.
Concomitant Medication collection	X	Within 14 days of randomization
Efficacy Assessments		
Radiographic Tumor Assessment (Chest, abdomen, pelvis)	X	Should be performed within 28 days of randomization. CT/MRI of brain (with contrast) should only be performed in subjects with a known history of treated brain metastases. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit and at subsequent on-study assessments.
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy (for IHC)	X	May be archival or recent sample. 1 formalin-fixed paraffin embedded tumor tissue block, or minimum of 10 FFPE unstained slides are needed. Specimens must be received by the central lab prior to subject randomization
Pharmacogenetic Sample (PGx)- Optional	X	Can be obtained at any time after Study and PGx Informed Consent is obtained.

Table 5.1B: On-Study Assessments ARM A (BMS-936558)

Procedure	C1D1	C1D8	Each cycle (Every 2 weeks) on Day 1(± 5 days)	Every Other Cycle (every 4 weeks) on Day 1(± 5 days)	Every 3 cycles (6 weeks ± 5 days)	Notes (add note on cycles)
Safety Assessments						
Vital Signs and Oxygen saturation	X	X	X			Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------continuously----------					Assessed using NCI CTCAE v. 4.0
Physical measurements (including Performance Status)	X	X	X			Includes Weight and ECOG status
Complete blood counts(CBCs) (Results obtained prior to dosing on infusion days)	X	X	X			Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	X	X	X			Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate, glucose), LDH

Table 5.1B: On-Study Assessments ARM A (BMS-936558)

Procedure	C1D1	C1D8	Each cycle (Every 2 weeks) on Day 1(± 5 days)	Every Other Cycle (every 4 weeks) on Day 1(± 5 days)	Every 3 cycles (6 weeks ± 5 days)	Notes (add note on cycles)
Liver Function Testing (Results obtained within **72** hours prior to dosing on infusion days)	X	X	X			Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin
Thyroid Function Testing	X				X	TSH (reflex to free T3 and free T4 if abnormal result)
Review of Concomitant Medications	X	X	X			Review at every visit
Pregnancy Test					X	Serum or urine (for WOCBP only) test to be performed **every 6 weeks)**

Table 5.1B: On-Study Assessments ARM A (BMS-936558)

Procedure	C1D1	C1D8	Each cycle (Every 2 weeks) on Day 1(± 5 days)	Every Other Cycle (every 4 weeks) on Day 1(± 5 days)	Every 3 cycles (6 weeks ± 5 days)	Notes (add note on cycles)
Efficacy Assessments						
Radiographic Tumor Assessment					X	Tumor assessments are conducted at Week 9 (±5 days) and every 6 weeks from Week 9 (±5 days), from randomization until documented disease progression or treatment discontinuation, whichever occurs later. Assessments should include chest and abdomen (with contrast) as well as any area that is being monitored. Follow RECIST 1.1 criteria.
Biomarker						
Serum (for soluble factors and miRNA Analyses)	X				X*	Must be obtained any time after randomization, prior to dosing C1D1 *In addition, ONE on -study serum sample will be obtained at Cycle 7 (± 5 days) ONLY
Whole Blood (for SNP testing)	X					Can be obtained on Day -3 to Day 1 prior to dosing
Pharmacokinetic and Immunogenicity Assessments (BMS-936558 Treatment Arm ONLY)	----------throughout study ----------					For detailed sample timing, see Table 5.1E in this Section 5.1

Table 5.1B: On-Study Assessments ARM A (BMS-936558)

Procedure	C1D1	C1D8	Each cycle (Every 2 weeks) on Day 1(± 5 days)	Every Other Cycle (every 4 weeks) on Day 1(± 5 days)	Every 3 cycles (6 weeks ± 5 days)	Notes (add note on cycles)
Patient reported outcomes (PRO) Assessment	X			X		**For C1D1**- performed after randomization PRIOR to first dose (day -3 to +1). **For on study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. Assessments will be performed at every other cycle on Day 1 (+/- 5 days) for the first 6 months on study, then every 6 weeks thereafter for the remainder of the study
Clinical Drug Supplies						
BMS-936558 (3 mg/kg)	X		X			Record Study Drug Infusion start and stop times.

Table 5.1C: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8 ± 5 days	Each Cycle every 3 weeks on Day1 (± 5 days)	Every 2 cycles (6 weeks ± 5 days)	Notes
Safety Assessments					
Vital Signs and Oxygen saturation	X	X	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical measurements (including Performance Status)	X	X	X		Includes weight (calculated BSA) and ECOG status
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------continuously----------				Assessed using NCI CTCAE v. 4.0
Complete blood counts(CBCs) (Results obtained prior to dosing on infusion days)	X	X	X		Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests	X	X	X		Includes Serum creatinine, blood urea nitrogen or serum urea level, sodium, calcium, magnesium, phosphate, potassium, chloride and bicarbonate, glucose, LDH
Liver Function Testing (Results obtained within 72 hours prior to dosing on infusion days)	X	X	X		Includes aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1C: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8 ± 5 days	Each Cycle every 3 weeks on Day1 (± 5 days)	Every 2 cycles (6 weeks ± 5 days)	Notes
Thyroid Function Testing	X			X	TSH (reflex to free T3 and free T4 if abnormal result)
Review of Concomitant Medications	X	X	X		Review at every visit
Pregnancy Test				X	Serum or urine (for WOCBP only) test to be performed every 6 weeks)
Efficacy Assessments					
Radiographic Tumor Assessment				X	Tumor assessments are conducted at Week 9 (±5 days) and every 6 weeks from Week 9 (±5 days), from randomization until documented disease progression or treatment discontinuation, whichever occurs later. Assessments should include chest and abdomen (with contrast) as well as any area that is being monitored. Follow RECIST 1.1 criteria.

Table 5.1C: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8 ± 5 days	Each Cycle every 3 weeks on Day1 (± 5 days)	Every 2 cycles (6 weeks ± 5 days)	Notes
Biomarker					
Serum (for soluble factors and miRNA Analyses)	X			X	Must be obtained any time after randomization, prior to dosing C1D1 In addition, ONE on -study serum sample will be obtained at Cycle 5 (±5 days) ONLY
Whole Blood (for SNP testing)	X				Can be obtained on Day -3 to Day 1 prior to dosing
Patient reported outcomes (PRO) Assessment	X		X		**For C1D1**- performed after randomization PRIOR to first dose (day -3 to +1). **For on-study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. Assessments will be performed at every cycle on Day 1 (± 5 days) for the first 6 months on study, then every 6 weeks thereafter for the remainder of the study.
Clinical Drug Supplies					
Docetaxel (75 mg/m^2)	X		X		Record Study Drug Infusion start and stop times. Dexamethasone 8mg PO BID (or institutional equivalent) on the day before, day of, and day after chemotherapy. Please use the institutional standard for dexamethasone dosing.

Table 5.1D: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose. X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
Radiographic Tumor Assessment	X*	X	For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed every 6 weeks (± 5 days) until PD, withdrawal of consent, death, lost to follow-up, or start of a subsequent anti-cancer therapy *Radiographic assessments for subjects who have not experienced PD ***must*** be obtained every 6 weeks (±5 days), and ***not*** delayed until X01 or X02.
Pharmacokinetic Assessments (BMS-936558 Arm ONLY)	X		For detailed sample timing, see Table 5.1E in this Section 5.1
Immunogenicity (BMS-936558 Arm ONLY)	X		
Patient reported outcomes Assessment (PRO)	X		

Table 5.1D: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose. X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
Safety Assessments			
Vital Signs	X		
Physical Measurements (including Performance Status)	X		
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	X	X*	*Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti cancer therapy.
Laboratory Tests	X		CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride, and bicarbonate), AST, ALT, total bilirubin, alkaline

Table 5.1D: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose. X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
			phosphatase, glucose, LDH, TSH (reflex to free T3 and free T4 if abnormal result)
Review of Concomitant Medications	X		
Collection of Survival Information	X	X	Every 3 months until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.

Table 5.1E: Pharmacokinetic and Immunogenicity Sample Collection from BMS-936558 Arm				
Study Day[a]	**Sampling Event (Relative To Time of Infusion) Hour**	**Time (Relative To Start of Infusion) Hour: Min**	**Pharmacokinetic Blood Sample Schedule**	**Immunogenicity Blood Sample Schedule**
C1D1	0 (Predose)	00:00	X	X
C1D1	1.0 (EOI)[b]	01:00	X	
C2D1	0 (Predose)	00:00	X	X
C3D1	0 (Predose)	00:00	X	X
C8D1	0 (Predose)	00:00	X	X
C8D1	1.0 (EOI)[b]	01:00	X	
Every 8th Cycle after C8D1 until discontinuation of study treatment	0 (Predose)	00:00	X	X
First 2 Follow-up visits- (up to 100 days from end of treatment visit- EXCEPT for subjects that WITHDRAW CONSENT)			X	X

[a] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow up visits.

[b] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration of 1 hour, the collection of this sample should also be delayed accordingly.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens

- Site manual for operation of interactive voice response system (randomization)
- Serious Adverse Event (or eSAE) case report forms
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide
- IRC manual
- ePRO manual

Each site will be provided with a touch screen electronic PC tablet for the subject's completion of the PRO questionnaires. Subjects will enter the data directly on to the electronic PC tablet at the time of the scheduled visits, prior to any study procedures and study drug infusion. There will not be any other source data or data entry for these questionnaires outside of what is on the tablet. The data will then be transferred to the ePRO vendor at specified time points throughout the study. (see schedule Table 5.1 B, 5.1C and 5.1D for frequency of assessments)

5.3 Safety Assessments

5.3.1 Screening Assessments (Baseline visit)

Screening assessments and procedures must be completed within 28 days of randomization, in accordance with Table 5.1A

- A complete medical history and concomitant medications
- Assessment of pretreatment signs and symptoms
- Patient reported outcomes Assessments (PRO): Lung Symptom Cancer Scale (LCSS) and EuroPRO Group's EQ-5D
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours of dosing
- Physical examination and physical measurements including height, and weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status
- Laboratory tests include (performed within 14 days prior to randomization):
  - Blood for complete blood count (CBC) with differential, including neutrophil and lymphocyte count
  - Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, glucose, LDH)

  - AST, ALT, total bilirubin, alkaline phosphatase, albumin
  - TSH, free T3 and free T4
  - Hepatitis B (HBV sAg) and Hepatitis C (HCV RNA)
- A pregnancy test for WOCBP will be collected within **24** hours prior to randomization

Signs and symptoms present within 14 days prior to randomization (regardless of relationship to disease) will be recorded. Additionally, record any concomitant medications taken within 14 days of randomization.

5.3.2 On-Study Safety Assessments and Procedures

The following assessments will be monitored according to the frequency for each treatment Arm starting on Cycle 1 Day 1 and will continue at the specified frequency until discontinuation from the study. (See Tables 5.1B and 5.1C for frequency of testing by treatment arm)

- Patient reported outcomes Assessments (PRO): Lung Symptom Cancer Scale (LCSS) and EuroPRO Group's EQ-5D
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) 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 (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 managment algorithm contained within the Investigator's Brochure.
- AEs and SAEs continuously throughout the study
- Physical examination and physical measurements including height, and weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results 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, bicarbonate, glucose, LDH)
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results obtained within 72 hours prior to dosing on infusion days)

- Thyroid function testing includes TSH (reflex to free T3 and free T4 if abnormal result)
- A pregnancy test for WOCBP will be performed every 6 weeks on study.

Concomitant medications taken throughout the study duration should be recorded within the eCRF.

Blood samples will also be collected for pharmacokinetics and immunogenicity as noted in Table 5.1E (for subjects randomized to the BMS-936558 treatment Arm A only), and for SNP testing as noted in Tables 5.1B and 5.1C.

Additionally, serum samples (for soluble factors and miRNA analyses) will be obtained from all randomized subjects prior to first dose of study drug, and during the study at Cycle 7, Day 1 (for the BMS-936558 arm) or at Cycle 5, Day 1 (for the docetaxel arm). (See Table 5.1B or Table 5.1C)

For subjects who discontinue study treatment due to toxicity, please follow the procedures for the last scheduled visit on study treatment (prior to discontinuation of study therapy and follow-up visits) from either Table 5.1B or Table 5.1C (and Table 5.1E -pharmacokinetic and immunogenicity samples for subjects randomized to BMS-936558 treatment Arm A only).

5.3.3 Follow-up and Survival Procedures

Subjects will be monitored for safety according to Table 5.1D. During the 100 days after the last dose of study treatment, subjects will have two follow-up visits for safety. Safety assessments will include: review of concomitant medications, physical examination, vital signs, ECOG performance status, laboratory measurements (CBC, serum chemistry, liver function and thyroid function), and assessment of signs and symptoms including AEs and SAEs. Beyond 100 days from the last dose of study treatment, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.

Blood samples will be collected for pharmacokinetics and immunogenicity as noted in Table 5.1E (only for subjects randomized to BMS-936558-at the first 2 follow-up visits up to 100 days from the end of treatment, except for subjects that withdraw consent).

Patient reported outcome (PRO) assessments (LCSS and EQ-5D) will be administered at the first two follow-up visits prior to any study related procedures and dosing.

Beyond the second follow-up visit, subjects should be followed for survival assessment every 3 months until death, lost to follow-up, or withdrawal of consent. The survival assessments may be performed by phone contact or an office visit.

5.4 Efficacy Assessments

5.4.1 Screening (Baseline visit) and On-Study Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1A, B, and C, according to RECIST 1.1 [59]. High resolution CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of randomization. In addition to chest, abdomen and pelvis, all known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks or as per local standard of care, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 beyond progression), lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 1 for details of RECIST 1.1).[59] All radiographic assessments performed for study purposes will be submitted to the IRC for adjudication of the primary and secondary efficacy endpoints.

5.4.2 Screening tumor tissue for PD-L1 Biomarker Analysis (archival or recent biopsy)

A formalin-fixed, paraffin-embedded tumor tissue block or unstained slides–of tumor sample (archival or recent) for biomarker evaulation must be available at screening for all subjects at study entry, and received by the central lab prior to subject randomization. In the case of unstained slides, a minimum of 10 slides are necessary to conduct the planned biomarker analyses. (Biopsies should be of reasonably sufficient size to ensure an adequate amount of tissue for analysis and should be excisional, incisional or core needle; fine needle aspiration is insufficient). If a recent biopsy has been collected and submitted, submission of archival tissue, if available, is still highly encouraged. Complete instructions on the collection, processing, handling, and shipment of all samples, including archival and fresh tumor biopsies, will be provided in a separate procedure manual.

A reference laboratory will receive the samples for immunohistochemistry (IHC) - based analyses aimed at determining the abundance of immunoregulatory proteins including PD-L1. The abundance of PD-L1 protein expression will be correlated with clinical efficacy endpoints. Additional exploratory analyses will be conducted as per Section 5.9.2.2.

5.4.3 Follow-up and Survival Procedures

Subjects who discontinue study treatment prior to progression, and subjects being treated beyond disease progression, will be followed with radiographic tumor assessments every 6 weeks (± 5 days) until documented or further disease progression, withdrawal of study consent, lost to follow-up, or beginning of a subsequent anti-cancer treatment. Radiographic assessments should be performed according to Section 5.4.1. All radiographic assessments performed for study purposes during the follow-up phase will be submitted to the IRC for adjudication of the primary and secondary efficacy endpoints.

Survival will be followed after progression, either by direct contact (office visits) or via telephone contact, according to Table 5.1D until death, withdrawal of study consent, or lost to follow-up.

5.4.4 Primary Efficacy Assessment

This study has co-primary endpoints of ORR (as assessed by the IRC) and OS. See section 8.3 for definitions of ORR and OS. All subjects will be monitored by radiographic assessment on an every-6-week schedule [beginning from the first on-study assessment on week 9 (±5 days)] to determine changes in tumor size according to Section 5.4.1. RECIST 1.1 criteria will be used for the assessment (see Appendix 1). For OS, every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.4.5 Secondary Efficacy Assessments

For secondary efficacy analyses (PFS as assessed by the IRC, clinical benefit in PD-L1+ versus PD-L1- protein expression subgroups, response duration, and time to response), subjects will be monitored by radiographic assessment on an every-6-week schedule [beginning from the first on-study assessment on week 9 (±5 days)], as for the primary efficacy assessment and according to Section 5.4.1. RECIST 1.1 criteria will be used for the assessment (see Appendix 1). Survival information will be collected as for the primary efficacy assessment.

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn only from study subjects randomized to the BMS-936558 treatment arm at the time points indicated in Table 5.1E. Blood samples should be drawn from a site other than the infusion site on days of infusion. All samples collected pre-dose should be taken just prior to the administration (predose) and end-of-infusion (EOI) samples should be taken just prior to EOI (preferably within 2 minutes prior to EOI) from the contralateral arm (ie, the arm not used for the infusion). If the infusion is interrupted, the reason for interruption will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70^{o}C

(samples may be stored at -20°C up to 2 months). Serum samples will be analyzed for BMS-936558 by a validated ELISA method. Further details on pharmacokinetic sample collection and processing will be provided to the site in a procedure manual.

5.6 Biomarker Assessments

Please refer to Section 5.8.2 and 8.4.5 for biomarker assessments and analyses. For the Pharmacogenetic information, please refer to the Pharmacogenetic Amendment 01, as applicable.

5.7 Outcomes Research Assessments

Patient reported outcomes (PRO) will be measured according to Tables 5.1B, C, and D, using the following two validated subject self-reported questionnaires: Lung Cancer Symptom Scale (LCSS), and EuroPRO Group's EQ-5D.

Subjects will be asked to complete questionnaires before any clinical activities are performed during visits to the study clinics at screening, on-study visits, and at the designated study visits in the follow-up (post-treatment) phase of the study.

Questionnaires will be provided in the subject's preferred language.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected from subjects randomized to the BMS-936558 treatment arm according to the schedule given in Table 5.1E. Samples will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemilumeminescent (ECL) immunoassay.

5.8.2 Exploratory Biomarker Assessments

A variety of factors that could potentially predict clinical response to BMS-936558 will be investigated in tumor specimens obtained at screening, and in peripheral blood taken both at screening (prior to first dose of study drug) and during the study, from all randomized subjects as outlined in Table 5.1A, B and C. Data from these investigations will be evaluated for associations with objective response, survival (OS, PFS), and/or safety (adverse event) data. Comparative analyses of markers between the two treatment arms will be used to identify biomarkers with predictive versus prognostic value.

Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual.

5.8.2.1 Peripheral Blood Markers

Serum-Soluble Factors:

Serum will be obtained from all randomized subjects prior to first dose of study drug, and during the study at Cycle 7, Day 1 (for the BMS-936558 arm) or at Cycle 5, Day 1 (for the docetaxel arm). To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of BMS-936558, the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be investigated by ELISA, seromics, and/or other relevant multiplex-based protein assay methods. Analyses may focus also on factors associated with NSCLC prognosis and/or responses to standard chemotherapeutic agents. Examples of analytes to be assessed include but are not limited to factors induced by IFNγ signaling (eg T cell chemoattractants CXCL9; CXCL10), antibodies to tumor-associated antigens, and soluble PD-L1 (sPD-L1), which may play an important role in immune tolerance and disease progression.

Serum miRNA:

MicroRNAs are broadly-expressed, small RNAs that regulate the abundance of mRNA transcripts and their translation into protein. Global miRNA expression profiling has become increasingly common in cancer research, and miRNA signatures that are correlated to stage of disease or to clinical outcomes are now available for a variety of cancer types. Expression profiling of miRNA may be useful also in identifying molecular markers for the prediction of drug-responses and for prospective stratification. Intriguingly, miRNAs are stable in serum and may represent miRNAs over-expressed in tumors and/or reflect immune system activity. Serum taken at baseline and during the study (as indicated in the subsection above) from subjects randomized to each treatment arm will be analyzed for miRNA content by microarray and/or by similar methodologies (eg quantitative RT-PCR). The resulting miRNA expression profiles will be evaluated for associations with response and survival data. Pharmacodynamic changes in miRNA expression also may be monitored. Of particular interest will be the expression of miRNAs that have been implicated in the regulation of genes involved in PD-1 signaling (eg miR-513, which has been shown to regulate PD-L1 and to act as part of an IFNγ-

induced signaling cascade) and how the expression of such miRNAs correlate with the expression of immunoregulatory proteins within tumors. Ultimately, this approach may lead to the identification of unique miRNA signatures that could be useful for identifying NSCLC subjects who are likely (or unlikely) to respond to BMS-936558 treatment.

Whole Blood SNP:

Whole Blood SNP: Whole blood will be collected from all subjects at C1D1 (can be obtained on Day -3 to Day 1 prior to dosing) to generate genomic DNA for candidate-based and/or whole-genome Single Nucleotide Polymorphism (SNP) analyses. Candidate-based analyses will focus on SNPs within genes associated with PD1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to BMS-936558 and/or with adverse events during treatment. A similar approach will be taken with putative genome-wide association studies (GWAS). Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically-relevant biomarkers identified by other methodologies described in this section.

5.8.2.2 Tumor Markers

A formalin-fixed, paraffin-embedded tumor tissue block or unstained slides (minimum 10 requested) of tumor sample (archival or recent) for biomarker evaluation will be obtained prior to subject randomization as outlined in Section 5.4.2. A reference laboratory will receive the samples for immunohistochemistry (IHC)-based analyses aimed at determining the abundance of the immunoregulatory proteins such as PD-1, PD-L1 and PD-L2. Additional immunohistochemical analyses may be completed to determine the abundance of other protein markers associated with TILS or with NSCLC disease progression. The abundance of each protein monitored (or combinations of proteins) will be correlated with clinical endpoints.

FFPET may be evaluated also by fluorescent in-situ hybridization (FISH), genetic mutation detection methods, and/or by RT-QPCR as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance to therapeutics used in the treatment of NSCLC. Such analyses will be completed retrospectively and within the scope of informed consent.

5.8.3 Healthcare Resource Utilization

Healthcare resource utilization data associated with hospitalizations and non-protocol specified medical visits related to either study therapy or disease will be collected for all randomized subjects. The healthcare resource utilization will be assessed during the study according to treatment arm assignments below:

- Treatment arm A (BMS-936558): Day 1 of cycle 3 and subsequently on Day 1 of every other cycle (every 4 weeks) on study treatment, and at the first 2 follow-up visits after discontinuation of study treatment.
- Treatment arm B (docetaxel): Day 1 of cycle 2 and subsequently on Day 1 of every cycle (every 3 weeks) on study treatment, and at the first 2 follow-up visits after discontinuation of study treatment

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires insubject hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing (within 30 days of last visit for enrollment/ screening failures). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee)

within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential drug induced liver injury is defined as

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see the Evaluation and Management Guidelines found in the Investigator Brochure.[20]

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Two independent committees will be utilized, a data monitoring committee (DMC) and an independent review committee (IRC).

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209017, and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for BMS-936558. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. Efficacy will also be reviewed by the DMC - as part of the benefit-to-risk assessment and for the formal analyses of overall survival (OS).

The DMC will be advisory to the clinical study leadership team. The clinical study leadership team will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes in study conduct are required.

After meeting, the DMC will notify the clinical study leadership group that it has met and will provide recommendations about the study by telephone or email. Detailed procedures to deliver and address the DMC recommendations are described in the BMS Standard Operating Procedure, which specifies the establishment and operation of

clinical trial DMCs. Any recommendation by the DMC regarding study modification will be submitted to the clinical study leadership team within pre-specified business days of the DMC meeting.

The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Details of DMC responsibilities and procedures will be specified in the DMC charter.

The IRC will review all available tumor assessment scans to determine response (RECIST 1.1). IRC-determined response will be used in the analyses of ORR and PFS. Details of IRC responsibilities and procedures will be specified in the IRC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size of the study accounts for the two co-primary efficacy endpoints: ORR and OS. ORR will be evaluated for treatment effect at the overall alpha of 0.01 (two-sided) with at least 90% power; no interim analysis of ORR is planned. OS will be evaluated for treatment effect at the overall alpha level of 0.04 (two-sided) with 90% power, accounting for one formal interim analysis to assess efficacy.

Approximately 264 subjects will be randomized to the two treatment arms in a 1:1 ratio. The study requires at least 189 deaths to ensure that a two-sided 4% significance level sequential test procedure with one interim analysis will have 90% power to detect a hazard ratio (HR) of 0.61, corresponding to a median OS of 7 vs. 11.4 months for the docetaxel and BMS-936558 treatment arms, respectively. Assuming a piecewise constant accrual rate (2 subjects/month during Month 0 - 1, 6 subjects/month during Month 1 - 2, 15 subjects/month during Month 2 - 4, 22 subjects/month during Month 4 - 6 and 30 subjects/month during Month 6 and thereafter), it will take approximately 24 months to obtain the required number of deaths for the final OS analysis (12 months for accrual and 12 months for survival follow-up). It is projected that an observed hazard ratio of 0.74 or less, corresponding to a 2.5 months or greater improvement in median OS (7 vs 9.5 months), would result in a statistically significant improvement in the final analysis of OS.

The final analysis of ORR, which requires a minimum follow-up of 6 months for all subjects, is projected to occur approximately 18 months after study initiation. This will

allow sufficient follow-up for ORR to have a stable estimate. Assuming ORR on docetaxel and BMS-936558 are 10% and 35%, respectively, 264 subjects will provide more than 90% power to detect a response rate difference of 25% with an overall two-sided type I error of 0.01.

One interim analysis of OS is planned at the same time of the final analysis of ORR (18 months after study initiation), which is projected to occur after 146 deaths (77% of total deaths) have been observed based on above accrual rate and the exponential distribution in each arm. The actual interim analysis will be conducted when two conditions are fulfilled: 1) a minimum follow-up of 6 months for all subjects and 2) at least 123 deaths (65% of total deaths) have been observed. This formal comparison of OS will allow for early stopping for superiority, and the boundaries for declaring superiority will be derived based on the actual number of deaths using Lan-DeMets α spending function with O'Brien and Fleming type of boundary in EAST v5.4. If the analysis is performed exactly at 146 deaths, the boundary for declaring superiority would be 0.016 (or 0.67 with regard to HR boundary, which corresponds to 3.4 months improvement in median OS under the assumed control arm hazard function). The boundary for declaring superiority for the final analysis after 189 events would be 0.035.

Table 8.1 summarizes the expected timing of each analysis.

Table 8.1: Schedule of Analyses

	Interim analysis for OS Final analysis for ORR	Final analysis for OS
Conditions	A minimum follow-up of 6 months and at least 123 deaths	At least 189 deaths
Expected timing	18 months (12 months accrual + 6 months follow-up)	24 months (12 months accrual + 12 months follow-up)
Alpha level	Final ORR at 0.01 level	
	Interim OS at 0.016 level[a]	Final OS at 0.035 level[a]

[a] Using Lan-DeMets α spending function with O'Brien and Fleming type of boundary when exactly 146 deaths are observed at the interim analysis for OS.

8.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All randomized subjects: All subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of efficacy and baseline characteristics
- All treated subjects: All subjects who received at least one dose of BMS-936558 or docetaxel. This is the primary dataset for dosing and safety
- PK subjects: All subjects with available serum time-concentration data from randomized subjects dosed with BMS-936558
- Immunogenicity subjects: All subjects with available data from randomized subjects dosed with BMS-936558
- Biomarker subjects: All subjects with available biomarker data from randomized subjects dosed with BMS-936558

8.3 Endpoint Definitions

8.3.1 Primary Endpoint

The primary objective in the study will be measured by the co-primary endpoints of ORR and OS.

The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects. BOR is defined as the best response designation, as determined by the IRC, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue BMS-936558 beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

8.3.2 Secondary Endpoints

The first secondary objective (to compare PFS as assessed by the IRC) will be measured by the key secondary endpoint PFS in each randomized arm. It is defined as the time from randomization to the date of the first documented tumor progression as determined by the IRC (per RECIST 1.1), or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

Assuming median PFS on docetaxel and BMS-936558 are 2.9 months and 5 months (HR = 0.58) respectively, approximately 245 PFS events will occur at the time of the final analysis of OS. This gives more than 90% power to detect a treatment difference of 2.1 months.

The second secondary objective (to evaluate clinical benefit in PD-L1+ and PD-L1- subgroups) will be measured by the same primary endpoints. ie, ORR and OS in subjects within PD-L1+ and PD-L1- subgroups.

The third secondary objective (to evaluate durability of and time to objective response) will be measured by secondary endpoints duration of objective response (DOOR) and time to objective response (TTOR) in each randomized arm. DOOR is defined as the time between the date of first response to the date of the first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last assessment. TTOR is defined as the time from randomization to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

The fourth secondary endpoint (to evaluate QoL) will be measured by secondary endpoint of disease-related symptom progression rate. It is defined as the proportion of randomized subjects who had a disease-related symptom progression as measured by the LCSS. The first six items of the LCSS are summarized into a symptom scale ranging in score from zero (0) to one hundred (100), with zero being the best possible score and 100

the worst possible score. The minimum important change in the LCSS used to define symptom progression is approximately a change of 10 mm in a Visual Acuity Scale (VAS), and that definition has been used for this NSCLC symptom scale in other trials. Disease-related symptom progression is defined as a subject increasing by 10 mm on the average LCSS VAS relative to the subject's baseline average LCSS score and then not going back down below that point for the remainder of the study. LCSS questionnaire is completed on Day 1 of the scheduled cycle for the first 6 months on study treatment, then every 6 weeks thereafter for the remainder of the study, and at the first two follow-up visits. See Tables 5.1B, and 5.1C (and Table 5.1D for Follow-up visits) for frequency of assessments on study for each treatment arm.

8.3.3 Exploratory Endpoints

Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of BMS-936558 and to explore exposure-safety and exposure-efficacy relationships.

Other exploratory endpoints for pharmacogenomics, immunogenicity and outcomes research are discussed in detail in Sections 8.4.5, 8.4.6, and 8.4.7.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Methods of Primary Endpoint

The comparison of IRC-determined ORR will be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior use of paclitaxel vs. no paclitaxel use, and region. An associated odds ratio and 99% CI will be calculated. Rates and their

corresponding 95% exact CI will be calculated by Clopper-Pearson method for each randomized arm. Sensitivity analysis based on investigator-determined ORR will also be performed.

The distribution of OS will be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by the same factors above. The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method. Survival rates at 6, 12, and 18 months will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood formula.

8.4.2.2 Methods for Secondary Endpoint

If either ORR or OS described above is positive, PFS in two randomized arms will be compared using a two-sided, log-rank test stratified by the same factors above. The significance level will correspond to the significance level of the co-primary endpoint comparisons that are positive (see details in the Statistical Analysis Plan). The HR and the corresponding two-sided (1-adjusted alpha) % CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each randomized arm will be estimated using the KM product-limit method. Two-sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method. Sensitivity analysis on PFS will also be performed.

Clinical benefits will also be evaluated in subjects within PD-L1+ and PD-L1- subgroups. ORRs and corresponding 95% exact CIs using Clopper-Pearson method, 95% CIs for the difference of rates using normal approximation, OS curves using KM method, and hazard ratios with corresponding 95% CIs using Cox proportional hazards model using randomized arm as a single covariate, will be provided for subjects within PD-L1+ and PD-L1- subgroups for each randomized arm. A logistic regression model will be used to test the interaction between PD-L1 expression status (positive vs. negative) and randomized arms for the ORR endpoint. The Interaction between PD-L1 expression status and randomized arms will be tested using Cox proportional hazards model for the

OS endpoint. All tests are descriptive and not adjusted for multiplicity. Other exploratory analyses, such as associations between PD-L1 status and other efficacy endpoints and evaluations of different thresholds for PD-L1 positivity, are also planned. See Section 8.4.6 for details.

The estimation of DOOR and TTOR in two randomized arms will be computed for subjects who achieve PR or CR using KM product-limit method. Median values of duration and time-to, along with two-sided 95% CI, will be calculated.

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, thyroid function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinisic covariates on the PK of BMS-936558 and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure-response analyses will be reported separately.

8.4.5 Biomarker Analyses

Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum obtained from subjects on each treatment arm, summary statistics for biomarkers of immunoregulatory activity (eg IFNγ-inducible proteins, miRNAs, antibodies to tumor antigens) and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit. In addition, the

time course of biomarker outcomes will be investigated graphically. If there is indication of a meaningful pattern across time, further analysis may be completed to characterize the relationship. Possible associations between changes in biomarker measures of interest and exposure to study drug will be explored graphically.

Pharmacogenomic and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to BMS-936558 and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily- as outlined in the exploratory objectives- on SNPs in select genes associated with immunity or on the expression of PD-1, PD-L1, and PD-L2 proteins in tumor specimens. Similar analyses will be completed with data regarding serum-soluble factors, serum miRNA content, and putative additional analyses to be completed using FFPET.

Associations between biomarkers and efficacy measures will be analyzed on all randomized subjects with available biomarker data. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg. response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

8.4.6 Outcomes Research Analyses

LCSS questionnaire complete rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point.

The disease-related symptom progression rate and its corresponding 95% exact CI will also be calculated by Clopper-Pearson method for each randomized arm. Same analysis will be conducted where the definition of disease-related progression will also allow for death and radiographic progression.

The EQ-5D will be used to assess the subject's overall health status. The following two measures from EQ-5D are used for this study: a population preference-based health state utility score (EQ-5D Index) and a subject's overall health state on a visual analog scale (EQ-VAS). Both the EQ-5D Index and the EQ-VAS have been shown to be reliable and valid for assessing health-related PRO in cancer subjects.[60 61 62] Summary statistics will be calculated for these 2 measures.

8.4.7 Other Analysis

Immunogenicity Analysis

A listing will be provided of all available immunogenicity data. Additionally, a listing of immunogenicity data from those subjects with at least one positive ADA at any timepoint will be provided. The frequency of subjects with at least one positive ADA assessment, and frequency of subjects who develop ADA after a negative baseline assessment will be provided. To examine the potential relationship between immunogenicity and safety, the frequency and type of AEs of special interest may be examined by overall immunogenicity status.

8.5 Interim Analyses

One interim analysis of OS is planned at the same time of the final analysis of ORR (18 months after study initiation), which is projected to occur after 146 deaths (77% of total deaths) have been observed based on above accrual rate and the exponential distribution in each arm. The actual interim analysis will be conducted when two conditions are fulfilled: 1) a minimum follow-up of 6 months for all subjects and 2) at least 123 deaths (65% of total deaths) have been observed. This formal comparison of OS will allow for

early stopping for superiority. Lan-DeMets α spending function with O'Brien and Fleming type of boundary will be used. The stopping boundary will depend on the actual number of deaths at the time of the interim analysis. However, if the analysis were performed exactly at 146 deaths, the boundary for declaring superiority would be 0.016. The boundary for declaring superiority for the final analysis after 189 deaths would be 0.035. An independent statistician external to BMS will perform the analysis.

In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the

amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) maintained at each study site where study drug and the following noninvestigation product(s) dexamethasone is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form,

respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator, and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic lymphoma kinase (CD246)
ALT	Alanine Aminotransferase
APC	Antigen-presenting cells
AST	Aspartate Aminotransferase
Bcl- x_L	B-cell lymphoma-extra large
BID	Twice per day
B7-DC	Human B7 –dendritic cell
B7-H1	Human B7 homolog 1
BMS	Bristol-Myers Squibb
BSC	Best supportive care
BTLA	B-and T-cell attenuator
CD28	Cluster of differentiation 28
CD273	Cluster of differentiation 273
CD274	Cluster of differentiation 274
C57BL/6	C57 black 6 breed mouse
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
COX2	Cyclooxygenase-2
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T-Lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP	Cytochrome P450
D	Day
DCF	Data clarification form
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DOOR	Duration of objective response

ECL	Electrochemilumeminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EI	Equivalence interval
ELISA	Enzyme-Linked Immunosorbent Assay Test
EOI	End-of-infusion
ESOI	Events of special interest
EU	European Union
FLIP	caspase-8 (FLICE)-like inhibitory protein
FSH	Follicle stimulating hormone
FU	Follow up
GCP	Good clinical practices
GMP	Good manufacturing practices
HCG	Human Chorionic Gonadotropin
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HTA	Health authority
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICOS	Inducible T-cell co-stimulator (CD278)
IDO	Inducible co-stimulator
IFN	Interferon
IFNGR1	Interferon Gamma-receptor-1
IFN-γ	Interferon Gamma
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL	Interleukin
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IRB/IEC	Institutional review board/independent ethics committee
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier curve

LMP	Low-molecular-mass protein
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
mg	Milligram
mL	Milliliter
MLR	Mixed Lymphocyte Reaction
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
M^2	Square meter
NCI	National Cancer Institute
NK	Natural killer
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NOS	Not otherwise specified
NOS2	Nitric oxide synthase 2
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PGE2	Prostaglandin E2
PK	Pharmacokinetics
PO	By mouth
P19	Serine-protease inhibitor
PR	Partial response
PRO	Subject reported outcomes
PSA	Prostate-specific antigen
PVG	Pharmacovigilance
q	Every
PRO	Patient reported outcomes
RAG	Recombination activating gene
RCC	Renal cell carcinoma

RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOC	System/Organ/Class
SOP	Standard operating procedures
Src	Sarcoma
STAT	Signal Transducers and Activators of Transcription
TAP1	Transporter associate with antigen processing 1
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIL	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRAIL	Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Treatment
Tregs	Regulatory T cells
TTOR	Time to objective response
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential

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APPENDIX 1 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ)

representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥10 mm but < 15 mm) should not be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the

vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in

protocols as ‘sufficient to require a change in therapy’. If ‘unequivocal progression’ is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a ‘new’ cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient’s brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Table 1 provides a summary of the overall response status calculation at each time point.

Appendix Table 1: Summary of the Overall Response Status Calculation [Time point response: patients with target (+/-) non-target disease]			
Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the

reappearance of an apparently ‘disappeared’ single lesion amongst many which remain is not in itself en ough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorisation is based upon the realisation that most lesions do not actually ‘disappear’ but are not visualised because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible ‘new’ disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009); 45:228-247.

APPENDIX 2 GUIDANCE ON CONTRACEPTION[1, 2, 3, 4, 5, 6, 7, 8]

ACCEPTABLE METHODS FOR PROTOCOLS WITH A NON-TERATOGENIC DRUG
(ANY SINGLE METHOD IS ACCEPTABLE)
Hormonal methods of contraception [a, b, c]
IUD [b, c, d]
Vasectomy [c, e]
Tubal Ligation [c]
Female or Male Condom with spermicide
Cervical Cap with spermicide
Diaphragm with spermicide

[a] Excludes progestin-only pills.

[b] Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The PK scientist and MST chair must agree that the use of hormone based contraception is safe and efficacious for WOCBP. The use of hormone based contraceptives is not otherwise restricted.

[c] A highly effective method of birth control with a failure rate less than 1% per year.

[d] IUDS used should have a failure rate less than 1%, (highly effective method) such as Mirena and ParaGard.

[e] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia.

Contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives.

UNACCEPTABLE METHODS OF CONTRACEPTION
Abstinence (including periodic abstinence)
No method
Withdrawal
Rhythm
Vaginal Sponge
Any barrier method without spermicide
Spermicide
Progestin only pills
Concomitant use of female and male condom

REFERENCES:

[1] Peterson Herbert B., et al. The risk of pregnancy after tubal sterilization: Findings from the U.S. Collaborative Review of Sterilization. Am J Obstet Gynecol. April 1996.

[2] Trussell, James. Contraceptive Failure in the United States. Contraception, 2004.

[3] Kestelman P., Trussell, J., Efficacy of the simultaneous use of condoms and spermicides. Fam Plann Perspect. 1991.

[4] Gabbay, Mark B. et al. A randomized crossover trial of the impact of additional spermicide on condom failure rates. Sexually Transmitted Diseases. October 2008.

[5] USAID, WHO and Marie Stopes International: Long-term contraceptive protection, discontinuation and switching behavior.

[6] Health Canada Guidance Document: "Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex." DRAFT-January 9, 2012

[7] MHRA: Clarification of contraceptive wording in clinical trials in the UK. Version 2-amended 21 May 2010.

[8] International Conference of Harmonization (ICH) Guidance for Industry M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, M3 (R2) January 2010.

Protocol Number: CA209017
IND Number: 100,052
Ex-US Non-IND
EUDRACT Number 2011-004792-36
Date: 12-Jun-2012
Revised Date: 25-Apr-2014

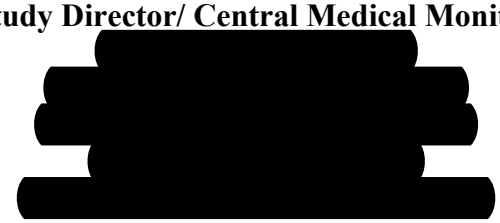
Clinical Protocol CA209017

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)

(**CheckMate 017**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **017**)

Revised Protocol Number: 03
Incorporates amendment(s): 09

Study Director/ Central Medical Monitor



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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 03	25-Apr-2014	Incorporates Amendment(s) 09 and Administrative Letter 1 dated 29-Aug-2013
Amendment 09	25-Apr-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). 1. Document history updated for Amend09 changes 2. Synopsis, Research Hypothesis: Updated to reflect the single primary endpoint of OS. 3. Synopsis, Objective(s): a) Primary Objective: Updated to remove ORR as a co-primary endpoint b) Secondary Objectives: Revised to add the first bullet related to ORR, and delete the original 3rd bullet on durability and time to objective response. 4. Synopsis, Figure 1 schema: Updated the primary and secondary endpoints and the original *footnote related to ORR and PFS 5. Synopsis, Study Assessments: Revised 2nd and 3rd paragaphs to reflect OS primary endpoint for the study and removal of ORR as a co-primary endpoint 6. Synopsis, Statistical Considerations: Revised wording in the Sample Size, Endpoints and Analyses sections to reflect OS as primary endpoint 7. Section 1- deletion of ORR reference in 4th paragraph, 2nd sentence. 8. Section 1.1.4- Deletion of last sentence referencing the IRC 9. Section 1.1.6- Revised the first sentence related to hypothesis 10. Section 1.2- Revised hypothesis to refer to OS and deleted any reference to ORR 11. Section 1.3.1- revised primary objective 12. Section 1.3.2- Revised Secondary objectives to reflect new hierarchy- ORR as first secondary objective; and deletion of another objective 13. Section 1.4- revised 4th sentence to reflect OS evaluation and deletion of ORR 14. Section 3.1- Revised primary and secondary endpoints, Figure 3.1-1, and additional wording in this section 15. Section 3.4.3- Revised language in second paragraph related to palliative radiotherapy 16. Section 3.6- Added a new last sentence to this section as part of the model document language 17. Section 4.3- Updated language in this section to reflect the current safety management algorithms

Document	Date of Issue	Summary of Change
		18. Section 4.3.2.2- Revised the second sentence 19. Section 5.1- Added a note * to the Tables 5.1-2 and 5.1-3 related to clinical drug supplies 20. Section 5.4.1- Revised information referring to the IRC 21. Section 5.4.3- Revised information referring to the IRC 22. Section 5.4.4- Revised the 1st sentence indicating primary endpoint 23. Section 5.4.5- Revised the last paragraph to reflect investigator-assessed ORR and PFS, and response language 24. Section 5.5- Revised language in the second to last sentence related to immunoassay and exploratory results 25. Section 5.8.1- Updated this section to add clarifying language regarding immunogenicity samples and analyses 26. Section 6.2.1- Added clarifying language as 3rd paragraph, related to collection timing of all non-serious AEs 27. Section 7- Revised the 1st sentence to remove IRC reference and deleted last paragraph related to IRC review 28. Section 8.1- Revised Table 8.1-1 and deleted all prior language related to the Schedule of Analyses 29. Section 8.2- Deleted bullets 5 and 6 and replaced with new bullets 5, 6, 7, 8, and 9 30. Section 8.3.1- Revised the language in the 1st sentence to reflect primary objective of OS 31. Section 8.3.2- Revised Secondary endpoints and added subsections 8.3.2.1, 8.3.2.2, 8.3.2.3, and 8.3.2.4 32. Section 8.4.2- Revised section to reflect the current hypothesis testing and primary endpoint of OS, as well as updated secondary endpoints. 33. Section 8.4.2.1- Added language to the 4th and 6th sentences 34. Section 8.4.2.2- Revised the section to reflect secondary endpoint changes to include ORR, removal of IRC assessment of PFS and other updates 35. Section 8.4.3- Updated the 2nd sentence in this section with MedRA reference 36. Section 8.4.6- Deleted the second paragraph 37. Section 8.5- Revised the language in this section to reflect new planned timing of interim analysis 38. Section 12- Updated references to add new references based on revisions 39. Appendix 1- Updated a typographical error in Section 2, 3rd paragraph, 4th sentence- to remove the word “not”.
Revised Protocol 02	29-May-2013	Incorporates Amendment(s) 07
Amendment 07	29-May-2013	1. The clinical CA209017 protocol is additionally identified as “CheckMate 017, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation” in the title page and Section 1.1. 2. The approved generic name “nivolumab” for BMS-936558 has

Document	Date of Issue	Summary of Change
		been added throughout the document. 3. Model Document template updates were made to Table names, to reflect new naming convention. 4. Synopsis was updated to be consistent with protocol changes in sections 1.3, 3.1, 3.3.1, 3.3.2. 5. Section 1.1.4 , last 2 sentences were updated with clarifying language. 6. Section 1.3.2 was revised to clarify the 2nd and 4th secondary objectives 7. Updated section 1.4.2.2, section 4.1 Table 4.1-1, sections 4.1.2. and 4.2.1 to add clarifying language on premedication for docetaxel. 8. Updated section 1.4.3.2 to add nephrotoxicity to the last paragraph, first sentence and additional safety information for opportunistic infections. 9. Updated Section 3.1, Figure 3.1-1 endpoints, updated information within the Treatment and Follow-up Phase sections, and revised the last paragraph in this section 10. Update section 3.3.1 Inclusion criteria 1b, 2b, 2ci through 2ciii, and 2g 11. Updated section 3.3.2 Exclusion criteria: Clarified exclusion criteria 1a, 2a, 2b, 2f, 3b, and revised exclusion criteria 6d to modify window of previous investigational agent to study dosing day 1 from 28 days to 14 days. 12. Added clarifying language in section 3.4.1 and section 3.4.2 13. Added clarifying language to section 3.4.3 to the first paragraph, related to permitted corticosteroids. Added clarifying language to second paragraph on corticosteroids and AEs considered related to radiotherapy needing resolution to ≤ Grade 1 14. Section 3.6; BMS Model document changes: Addition of 3 new subsections as part of the new model document: Addition of section 3.6 (Post Treatment Study Follow-up, Section 3.6.1 (Withdrawal of Constent) and section 3.6.2 (Lost to Follow-up) 15. Section 4.1, Study Treatments: Updated treatment initiation timing from randomization 16. Updated section 4.3., Selection and Timing of Dose for each Subject: Updated 1st and 2nd paragraphs, and modify dose calculation guidance for each treatment cycle. 17. Clarified wording in section 4.3.1 18. Clarified 1st sentence in second paragraph in section 4.3.2.2 19. Added clarifying language to section 4.3.4 on treatment discontinuation upon further progression 20. Updated section 4.3.5.1 with the FDA request for treatment discontinuation in event of a Grade 3/4 uveitis, or pneumonitis 21. Updated section 4.3.5.2 3rd bullet point 22. Updated the on-study Tables 5.1-1, 5.1.-2 , 5.1-3 and 5.1-4 with clarifying language related to table headers (windows for procedures and visits), testing frequency, notes. New procedures

Document	Date of Issue	Summary of Change
		have also been added, related to biomarker samples and PRO. 23. Updated section 5.2, last paragraph 24. Updated sections 5.3.1, 5.3.2, and 5.3.3 with clarifying language for on study and follow-up/ survival assessments 25. Deleted 3rd bullet in section 5.3.1 as first PRO assessment occurs at C1D1, 26. Updated Section 5.4.1 Updated first and second paragraphs referring to radiographic assessments and timing 27. Updates Section 5.4.2 to add a sentence to 1st paragraph 28. Updated Sections 5.4.3 and 5.4.4 with revised language. 29. Updated section 5.4.5 secondary efficacy assessment 1st sentence 30. Section 5.5, Pharmacokinetic Assessments: Updated the second to last sentence in the paragraph 31. Updated sections 5.7, and 5.8.1 with revised language 32. Section 5.8.2.1, Peripheral Blood Markers: Updated this section to include Peripheral Blood Mononuclear Cells (PBMC) and Peripheral Blood RNA as two new paragraphs, after the Whole Blood SNP paragraph 33. Updated section 8.1 with clarifying language. 34. Updated section 8.2 with clarified language to the 1st, 2nd and last bullets for population for analysis 35. Updated second paragraph in section 8.3.1 and revised language throughout section 8.3.2 36. Updated section 8.4.2.1 adding term "confirmed" to the ORR 37. Updated section 8.4.2.2 to clarify secondary endpoints 38. Updated Section 8.4.3, Safety Analyses: Deleted the words "treatment emergent" from the third sentence in this paragraph, for further clarification 39. Updated sections 8.4.6 and 8.4.7 to add revised language 40. Updated Appendix 1 to add new section 4.3. for Best Overall Response; All timepoints. 41. Included additional clarifications and corrections to typographical errors throughout the document.
Revised Protocol 01	08-Mar-2013	Incorporates Amendment(s) 06
Amendment 06	08-Mar-2013	Section 1.4.3.2 Safety Summary was updated to include language on preliminary new non-clinical safety findings of adverse pregnancy outcomes Section 3.3.1 Criteria 3a and 3d were updated to add clarifying language related to duration of contraception Section 12 was updated to add a new reference (57) Appendix 2 was updated to revise the acceptable methods table, and add new language at the end of the appendix.
Original Protocol	12-Jun-2012	Not applicable

SYNOPSIS

Clinical Protocol CA209017

Protocol Title: Protocol CA209017: 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)

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): For subjects randomized to BMS-936558 (nivolumab), BMS-936558 (nivolumab) will be 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 will be dosed intravenously over 60 minutes at 75mg/ m² every 3 weeks until disease progression, unacceptable toxicity or other reasons specified in the protocol.

Study Phase: 3

Research Hypothesis: BMS-936558 (nivolumab) increases OS as compared with docetaxel, in squamous cell NSCLC subjects treated with prior platinum doublet-based chemotherapy.

Objective(s):

Primary Objective: To compare the OS of BMS-936558 (nivolumab) versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy.

Secondary Objectives: Secondary objectives include the following:

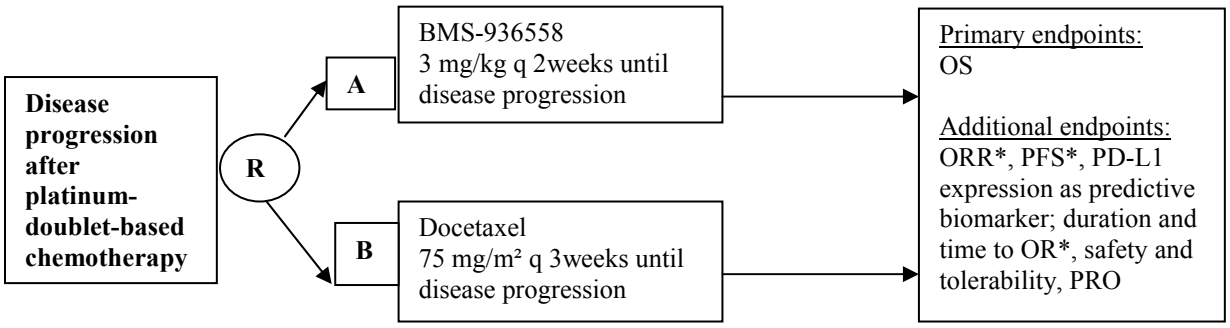
- To compare the ORR of BMS-936558 (nivolumab) versus docetaxel
- To compare the progression-free survival (PFS) of BMS-936558 (nivolumab) versus docetaxel
- To evaluate whether PD-L1 expression is a predictive biomarker for OS, ORR, or PFS
- To evaluate the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks, as measured by LCSS, in BMS-936558 (nivolumab) and docetaxel groups

Additional Exploratory objectives are listed in Section 1.3.3 of the protocol.

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 264 subjects will be randomized to BMS-936558 (nivolumab) vs docetaxel in a 1:1 ratio.

Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment arms (see Study Design and Duration schema in Figure 1 below). Randomization will be stratified and balanced according to the following factors: prior paclitaxel vs. no paclitaxel and region (US vs Europe vs Rest of World).

Figure 1: **Study Design**



* Objective Response and progression (by RECIST 1.1) as determined by investigator

Study Population:

Subjects must meet all eligibility criteria specified in Sections 3.3.1 and 3.3.2 of the protocol, including the following:

Key Inclusion Criteria (See Protocol Section 3.3.1 for full list of criteria)

1. Men and women ≥ 18 years of age
2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1
3. 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).
4. Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.(see protocol Section 3.3.1 for details)
    a. Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.
    b. 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.
    c. 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.
5. Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization
    a. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site
6. A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. 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 (See Protocol Section 3.3.2 for full list of criteria)

1. 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).
2. Subjects with carcinomatous meningitis
3. 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.
4. 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.
5. 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).
6. Prior treatment on the first-line study CA184104
7. Prior treatment with docetaxel
8. Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
9. Other active malignancy requiring concurrent intervention
10. 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
11. 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.
12. 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
13. Treatment with any investigational agent within 14 days of first administration of study treatment

Study Assessments: 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 chemotherapy. Subjects will be randomized to BMS-936558 (nivolumab) vs Docetaxel in a 1:1 ratio.

The primary endpoint for the study is OS.

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known alive date. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subjects discontinue the study drugs. All randomized subjects will be evaluated.

Statistical Considerations:

Sample Size:

The sample size of the study accounts for the primary efficacy endpoint, OS.

The final analysis of OS will be conducted when at least 231 deaths have been observed among 272 randomized subjects. Given the observed accrual and the survival assumptions it is expected that the duration of the study from start of randomization to final analysis will be approximately 38 months. One formal interim analysis for superiority of OS is planned after 196 deaths (85% of deaths required for final analysis) have been observed.

Endpoints:

The primary objective in the study will be measured by the primary endpoint of OS.

Key secondary endpoints include investigator-assessed objective response rate (ORR), and progression-free survival (PFS).

Analyses:

Efficacy Statistical Analyses:

All hypothesis testing will be two-sided based on a significance level of 0.05 except for OS. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses (overall alpha=0.05). If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1.) ORR

2.) PFS

The formal statistical testing for ORR will take place only if OS is statistically significant and the statistical testing for PFS will take place only if both OS and ORR are statistically significant. See Section 8.4.2 of the protocol for additional information.

The distribution of OS will be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by the same factors above. The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha)% confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). Survival rates at 6, 12, 18, 24, 36, 48 months and 5 year will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

The comparison of ORR will be carried out using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by above factors. An associated odds ratio and 95% CI will be calculated. ORR and their corresponding 95% exact CI will be calculated by Clopper-Pearson method for each randomized arm.

Summary statistics of time to objective response (TTR) will be provided for each treatment group for subjects who achieve PR or CR. Duration of response (DOR) in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

The distribution of PFS will 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 region (US vs Europe vs Rest of World).

HR and corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each treatment group will be estimated using the KM product-limit method. Two sided, 95% confidence intervals for median PFS will be computed by Brookmeyer and Crowley method- using a log-log transformed CI for the survivor function S(t). PFS rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the PFS curve for each randomized arm provided minimum follow-up is longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

Other secondary endpoints include PD-L1 expression as a predictive biomarker for efficacy endpoints and disease-related symptom progression rate. Statistical analyses for these endpoints are discussed in Section 8.4.

Safety Statistical Analysis:

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by

treatment arm. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be 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 will be summarized using worst grade per NCI CTCAE v4.0 criteria.

PK and Biomarker Analysis:

Serum samples will be collected to characterize pharmacokinetics of BMS-936558 (nivolumab) and to explore exposure-safety and exposure-efficacy relationships. A variety of factors that may impact the immunomodulatory properties and efficacy of BMS-936558 (nivolumab) will be investigated in peripheral blood, and in tumor specimens taken from all subjects prior to treatment. Data from these investigations will be evaluated for associations with response, survival, and/or safety data.

TABLE OF CONTENTS

1 INTRODUCTION AND STUDY RATIONALE

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths [1]. Despite treatment with platinum- and taxane-based chemotherapy, patients with metastatic NSCLC have a median survival of approximately 10 months, and a 5-year survival rate of approximately 15%.[2] Unlike patients with non-squamous histology NSCLC, patients with squamous cell NSCLC have generally not benefitted from (and in fact may be negatively impacted by) several new agents, including pemetrexed and bevacizumab. [3,4] Therapeutic options for squamous cell NSCLC are particularly limited after failure of front-line chemotherapy. Therefore, while representing a minority of NSCLC cases, squamous cell NSCLC remains a disease with high burden and unmet medical need.

Immunotherapeutic approaches for the treatment of malignancy recently have demonstrated clinical efficacy in several cancer types, including melanoma and hormone-refractory prostate cancer.[5] Tumors may modulate and evade the host immune response through a number of mechanisms, including downregulation of tumor-specific antigen expression and presentation, secretion of anti-inflammatory cytokines, and upregulation of inhibitory ligands. T cell checkpoint regulators such as CTLA-4 and programmed death-1 (PD-1, CD279) are cell surface molecules that, when engaged by their cognate ligands, induce signaling cascades down-regulating T cell activation and proliferation. One proposed model by which therapeutic T cell checkpoint inhibitors derive antitumor activity is through breaking of immune tolerance to tumor cell antigens.

BMS-936558 (nivolumab) is a fully human, IgG4 (kappa) isotype mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby purportedly abrogating inhibitory signals and augmenting the host antitumor response. In early clinical trials, BMS-936558 (nivolumab) has demonstrated activity in several tumor types, including melanoma, renal cell cancer (RCC), and NSCLC[6]. In particular, substantial activity has been noted in the squamous histology subgroup, where objective response rates approached ~40-50%, and progression free survival approached ~6 months.[7] In general, BMS-936558 (nivolumab) also has been well tolerated to date, with a favorable safety profile relative to anticipated toxicities based on an immunostimulatory mechanism of action.[8]

CA209-017 is a randomized, open-label, multinational Phase III trial of BMS-936558 (nivolumab) monotherapy versus docetaxel in subjects with squamous cell NSCLC whose disease has progressed during or after one prior platinum-based doublet chemotherapy regimen. The central question of the study will be to determine if BMS-936558 (nivolumab) improves overall survival (OS) over the comparator in this patient population. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of BMS-936558 (nivolumab) in subjects with squamous cell NSCLC.

1.1 Study Rationale

1.1.1 Rationale for BMS-936558 Monotherapy

PD-1 is a 55 kD type I transmembrane protein primarily expressed on activated T cells, B cells, myeloid cells, and antigen presenting cells (APC).[9] Binding of PD-1 to PD-L1 and PD-L2 has been shown to down-regulate T-cell activation in both murine and human systems.[10,11,12,13] In particular, PD-L1 has been shown to be upregulated on several cancers types including NSCLC and, in some cases, correlated to negative prognosis.[14,15,16,17,18] PD-1/PD-L interactions may also indirectly modulate the response to tumor antigens through T-cell/APC interactions. Therefore, PD-1 engagement may represent one means by which tumors evade immunosurveillance and clearance.[19] Blockade of the PD-1 pathway by BMS-936558 (nivolumab) has been studied in a variety of preclinical in vitro assays, and antitumor activity using a murine analog of BMS-936558 (nivolumab) has been shown in a number of immunocompetent mouse cancer models.[20] Based on these and other preclinical data, PD-1 blockade by BMS-936558 (nivolumab) has been pursued as a promising therapeutic strategy to reverse immune tolerance and enhance T-cell effector function in several tumor types including NSCLC.

Substantial monotherapy clinical activity has been observed in ≥ second line NSCLC subjects treated in the ongoing Phase 1 study of BMS-936558 (nivolumab) (CA209003), and in particular in subjects with squamous cell NSCLC (see Section 1.4.3.3). This study showed objective response rates (ORR) greater than the historical ORR for docetaxel (approximately 8-10%).[21,22,23] Preliminary estimates of median duration of response for NSCLC subjects in CA209003 approached 6 months, indicating response durability. Conversely, the historical median progression-free survival (PFS) for docetaxel is approximately 3 months.[21,22,23] Furthermore, the adverse event profile for BMS-936558 (nivolumab) appears favorable versus docetaxel, as hematologic toxicities are currently rare and the majority of non-hematologic toxicities are low grade and manageable. Therefore, CA209017 (CheckMate 017, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) will test the efficacy and safety of BMS-936558 (nivolumab) as monotherapy in previously treated squamous cell NSCLC.

1.1.2 Rationale for the use of docetaxel as a comparator

Docetaxel is one of several agents that are approved for use upon progression from first line therapy in NSCLC based upon improvements in PFS and OS when compared to best supportive care (BSC)[21] or active chemotherapies.[22] It has been used as a benchmark comparator vs. pemetrexed in a non-inferiority trial where PFS and OS in the docetaxel arm were 2.9 months and approximately 8 months, respectively.[23] Pemetrexed has not been approved for use in squamous cell NSCLC due to its relative lack of efficacy. Erlotinib is another agent that has been studied in second line squamous and non-squamous NSCLC; however, its uptake has not been universal in the squamous population. Docetaxel was therefore chosen as the comparator for this study, due to its clinical activity and lack of other suitable second line options in subjects with squamous cell NSCLC.

This study will stratify and balance the arms for prior paclitaxel use to make sure that the control arm is not affected by any possibility of cross-resistance. Use of docetaxel was studied in multiple trials after the use of combined agents, one had no prior paclitaxel use permitted[21], while the other had up to 42% of subjects receiving prior paclitaxel therapy.[22] The response rates and survival was equivalent. In addition, there was no reduced activity in the second-line use of docetaxel when compared with pemetrexed in the non-inferiority study despite 25% of all subjects receiving prior treatment with paclitaxel/platinum doublets.[23] The efficacy difference was not noted in other studies where docetaxel was used in combination with gemcitabine in the second-line and the majority of subjects received paclitaxel/platinum doublets in the first line.[24,25,26] Based on these data, subjects who received prior paclitaxel will be allowed onto the study, but will be stratified across the two treatment groups.

1.1.3 Rationale for BMS-936558 dose and schedule

The dose and schedule of BMS-936558 (nivolumab) in this study will be 3 mg/kg every 2 weeks, based upon a February 24, 2012 analysis of safety, efficacy, and exposure-response data from the ongoing Phase 1 study CA209003. Anti-tumor activity was observed in NSCLC subjects at dose levels of 1, 3 and 10 mg/kg every 2 weeks. Anti-tumor activity appeared to approach a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of exposure-response analyses showed that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg administered every 2 weeks. BMS-936558 (nivolumab) was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. While the spectrum, frequency, and severity of BMS-936558 (nivolumab) -related AEs were generally similar across the dose levels tested, the 10 mg/kg dose level had numerically higher rates of Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based on these observations, a dose of 3 mg/kg every 2 weeks was chosen for further study. Further information on observed safety, efficacy and pharmacokinetic data from CA209003 is reviewed in Section 1.4.3.

1.1.4 Rationale for Initial Tumor Assessment at 9 weeks

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in the Phase 1 CA209003 study of BMS-936558 (nivolumab). Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size appearing as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Another hypothesis is that the kinetics of tumor growth may initially outpace anti-tumor immune activity in some individuals. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. For these reasons, the initial tumor assessment in CA209003 was conducted at 8 weeks, and it is unknown if an earlier assessment would demonstrate similar activity due to premature termination of study treatment.

To mitigate the risk of detecting false-progression early in the course of treatment with BMS-936558 (nivolumab), the initial tumor assessment for both arms in this study will take place at Week 9 (± 5 days). Thereafter, all subsequent tumor assessments will take place regularly every 6 weeks (± 5 days) in both treatment arms.

1.1.5 Rationale for collection of tumor tissue and evaluation of tumor PD-L1 expression as a potential predictive biomarker

Aberrant expression of PD-L1 protein by tumor cells (retrospectively detected by IHC) has been reported in a number of human malignancies, especially in relation to poor prognosis, in multiple tumor types including squamous and non-squamous NSCLC .[14,15,16,17,18,27,28,29] In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells is related to tumor aggressiveness [16,30] and subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from cancer than subjects exhibiting low levels of PD-L1 expression. These findings may be explained by the notion that high PD-L1 expression leads to immune evasion. This hypothesis is supported by separate studies demonstrating that PD-L1 expressed by tumor cells enhances apoptosis of activated tumor-specific T cells in vitro and that the expression of PD-L1 protects tumor cells from the induction of apoptosis by effector T cells. In NSCLC, blocking PD-L1 allows for the increase of tumor-infiltrating CD8+ T cells and an increased production of IFN-γ but no difference noted in peripheral blood CD8+ T cells when subjects with NSCLC were compared with healthy controls.[31] These high levels of PD-L1 protein expression in NSCLC are also associated with poor prognosis and the presence of tumor infiltration by immature dendritic cells.[32]

Preliminary data indicate PD-L1 protein expression in tumors may correlate with BMS-936558 (nivolumab) clinical activity. Sixty-one pretreatment tumor specimens from a limited subset (N=42) of subjects in CA209003 (18 melanoma, 10 non-small-cell lung, 7 colorectal, 5 renal-cell, and 2 prostate cancer) were analyzed for tumor cell surface PD-L1 expression. Biopsy specimens from 25 of 42 subjects were positive for PD-L1 expression by IHC. Among these subjects, 9 (36%) achieved an OR. Among 17 subjects with PD-L1-negative tumors, none achieved an OR. This analysis is based on optional biopsies from a non-random subset of the population, and testing of a statistical hypothesis was not pre-specified. These preliminary results must, therefore, be interpreted with caution. Importantly, only 10/42 subjects in this subset had NSCLC, with only one responder in the PD-L1+ group. Therefore, these data are not conclusive as to the positive or negative predictive value of PD-L1 expression in NSCLC, and further analyses of a larger number of samples from CA209003 are planned.

In order to more thoroughly assess the role of PD-L1 protein expression as a predictive biomarker, archival or recent tumor tissue will be collected prospectively from all randomized subjects in this study, and a retrospective analysis of efficacy by PD-L1 expression status will be conducted. Due to the preliminary nature of the Phase 1 data and current lack of a verified IHC assay, subjects enrolled to CA209017 will not be selected or stratified by PD-L1 expression status. However, based on preliminary PD-L1 prevalence estimates in NSCLC of approximately 45-70% [17] (and unpublished data), a reasonable number of PD-L1 positive subjects are

anticipated to accrue to each treatment arm for the analysis. Additionally, the sponsor is in the process of developing a verified IHC assay that can be used to reproducibly measure PD-L1 expression in tumor tissue. Contingent on development of an optimized assay, future prospective analyses of PD-L1 expression and clinical outcome are planned.

1.1.6 Rationale for Patient Reported Outcomes Evaluation

Due to the proposed increase in ORR, OS, and PFS from treatment with BMS-936558 (nivolumab) relative to docetaxel, it is hypothesized that the proportion of subjects exhibiting disease-related symptom improvement, as measured by the Lung Cancer Symptom Scale (LCSS) will also increase related to BMS-936558 (nivolumab) over docetaxel. The EQ-5D will be used to assess general health status and the data will be used to calculate utilities for use in economic models.

1.2 Research Hypothesis

BMS-936558 (nivolumab) increases OS as compared with docetaxel, in squamous cell NSCLC subjects treated with prior platinum doublet-based chemotherapy.

1.3 Objectives

1.3.1 Primary Objective

To compare the OS of BMS-936558 (nivolumab) versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum doublet-based chemotherapy

1.3.2 Secondary Objectives

- To compare the ORR of BMS-936558 (nivolumab) versus docetaxel
- To compare the progression-free survival (PFS) of BMS-936558 (nivolumab) versus docetaxel
- To evaluate whether PD-L1 expression is a predictive biomarker for OS, ORR or PFS
- To evaluate the proportion of subjects exhibiting disease-related symptom improvement by 12 weeks, as measured by LCSS, in BMS-936558 (nivolumab) and docetaxel groups

1.3.3 Exploratory Objectives

- To assess the overall safety and tolerability of BMS-936558 (nivolumab) versus docetaxel
- To explore potential predictive biomarkers of BMS-936558 (nivolumab) efficacy (such as ORR, PFS and OS) in peripheral blood and tumor specimens, including antibodies to tumor antigens and proteins involved in regulating immune responses (eg, PD-1, PD-L1, PD-L2)
- To assess the effects of natural variation single nucleotide polymorphism (SNPs) in select genes (eg, PD-1, PD-L1, PD-L2, CTLA-4) has on clinical endpoints and/or on the occurrence of adverse events
- To characterize pharmacokinetics of BMS-936558 (nivolumab) and explore exposure-response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints

- To characterize immunogenicity of BMS-936558 (nivolumab)
- To assess the subject's overall health status using the EQ-5D Index and visual analog scale.

1.4 Product Development Background

BMS-936558 (nivolumab) is in clinical development for the treatment of subjects with NSCLC, renal cell carcinoma (RCC) and melanoma. An initial registrational opportunity for BMS-936558 (nivolumab) in NSCLC is focused on monotherapy in the second-line setting, after a subject has received a platinum-based combination. This will be evaluated through two studies, CA209017 in a squamous population and CA209057 in a non-squamous population. In CA209017, OS of BMS-936558 (nivolumab) will be evaluated as compared with docetaxel in subjects with squamous histology NSCLC. Other studies to be conducted in the NSCLC program will assess the efficacy of BMS-936558 (nivolumab) in additional lines of therapy, as monotherapy and/or in various combinations.

1.4.1 Mechanism of Action of BMS-936558

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses.[33,34,35] Support for the role of immunosurveillance in NSCLC is suggested in retrospective analyses demonstrating a correlation between tumor infiltrating lymphocytes in surgically resected specimens and recurrence free survival.[36,37,38] Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[39] Collectively, these signals govern the balance between T-cell activation and tolerance. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA[29]. PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon -γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes [40]. These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

In vitro, BMS-936558 (nivolumab) binds to PD-1 with high affinity (EC50 0.39-2.62 nM), and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ~ 1 nM). BMS-936558 (nivolumab) binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by BMS-936558 (nivolumab) results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV-re-stimulation assay with human PBMC, the effect of BMS-936558 (nivolumab) on antigen specific recall response indicates that BMS-936558 (nivolumab) augmented IFN-γ 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 BMS-936558(nivolumab) enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[20]

1.4.2 Non-small cell lung cancer (NSCLC) - Background and Treatments

Lung cancer is the leading cause of cancer-related deaths globally. An estimated 221,130 new cases of lung cancer will be diagnosed in 2011.[2] The majority of subjects (approximately 78%) are diagnosed with advanced or metastatic disease. Progression after first-line therapy occurred in nearly all of these subjects and the 5 year survival rate is only 3.6% in the refractory setting. [2] There is a particular unmet need among patients who have squamous cell NSCLC (representing up to 25% of all NSCLC) as there are few treatment options after first-line therapy (ie, pemetrexed is not a treatment option and erlotinib was not separately evaluated in a squamous cell subset of patients).[3,24] In addition, there are several targeted therapeutics that are restricted to the non-squamous population due to adverse events (ie, bevacizumab which caused fatal hemorrhage in squamous cell subjects).[4] According to NCCN guidelines, the use of single agent chemotherapy is standard-of-care for patients with recurrent and metastatic NSCLC after failure of platinum-based therapy.[2] Historical median PFS rates in second-line NSCLC are approximately 2.6 - 3.2 months, and median OS rates approximately 6.7 to 8.3 months (longer in the recent ZODIAC trial, 10+ months). [22,23,24,41,42] Current therapy in second-line includes docetaxel, erlotinib and pemetrexed (only in non-squamous histologies).[22,23,24] No agent has shown superiority in OS when compared to docetaxel. Different docetaxel schedules (other than the standard q3 weeks), chemotherapy doublets using docetaxel, and other comparative agents have not shown improvement over docetaxel in this line of therapy. [43,44,45,46,47]

1.4.2.1 Squamous cell NSCLC

Among the different histologies of NSCLC, squamous histology typically represents 25% of all lung cancer cases.[48] Most studies involving first-line and second-line therapy did not specifically separate subjects by histology, although this was recorded in all of the pivotal trials.[3,22,23,24] The first study that showed a difference in histology involved the comparison of gemcitabine and cisplatin to pemetrexed and cisplatin. In this study, subjects with squamous cell NSCLC had a median survival time of 10.8 months with the gemcitabine combination while it was only 9.4 months with pemetrexed. This is compared with the median survival time of 10.9 months with gemcitabine versus 12.6 months with pemetrexed in adenocarcinoma and 6.7 months with

gemcitabine versus 10.4 months with pemetrexed in large cell lung cancer.[3] A subanalysis of the pemetrexed non-inferiority study in second-line therapy[23] showed a statistically significant improvement in the combined non-squamous histologies when compared with docetaxel (9.3 months vs. 8.0 months (HR 0.778)) but not in squamous (6.2 months vs. 7.4 months (HR 1.563))[49]. Additional data has shown that there is a poorer prognosis among subjects with squamous cell NSCLC due to comorbidities related to smoking history, larger tumors with lymphatic and vascular invasion, and the presence of more poorly differentiated tumors although the risk of disease recurrence after initial treatment is the same between adenocarcinoma and squamous cell.[50]

The treatment of NSCLC has also been defined by the development of understanding of somatic mutations that drive tumor growth and development. For example, significant clinical benefit was noted among subjects with EGFR mutations when treated with EGFR TKIs [51,52]. However, low responses were noted among male smokers with squamous cell lung cancer when they were treated with erlotinib as compared with subjects who were female, nonsmokers and with adenocarcinoma.[53] It has been noted that EGFR mutations were observed in only 2.7% of squamous cell samples [54] and EGFR testing is not recommended in the NCCN guidelines.[2] Recently, analysis of genetic changes in squamous cell lung cancer has shown multiple potential targets for new drugs but this remains immature.[55]

Currently, second-line treatment for squamous cell lung cancer remains an area of unmet need. Docetaxel remains the benchmark treatment [2] in this line of therapy although erlotinib may also used with less frequency.

1.4.2.2 Docetaxel (Taxotere®)

Docetaxel is a cytotoxic microtubule inhibiting antineoplastic agent in the taxane class that is indicated as single agent treatment for locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy. Docetaxel is recommended to be administered in a facility equipped to manage possible complications such as anaphylaxis. The dosing is recommended at 75 mg/m² administered intravenouosly over one hour on an every 3 week schedule. A premedication of corticosteroids is given with each cycle of docetaxel, using an institutional standard regimen that is consistent with (or equivalent to) recommendations contained within the docetaxel label. [56]

1.4.2.3 Safety of docetaxel

The major adverse events related to docetaxel are primarily hematologic. The key grade 3 to 4 hematologic toxicities include neutropenia (30 - 67%), anemia (2 - 5%) and thrombocytopenia (< 1 - 2%). Non-hematologic adverse events related to docetaxel include febrile neutropenia (4.7 - 12.7%), asthenia (47 - 55%), alopecia (35%), nausea (26 - 36%), diarrhea (12-36%), peripheral neuropathy (15 - 24%), vomiting (17%), and fluid retention (5 - 16%).[21 22 23 42 47 56]
Warnings related to docetaxel include treatment-related mortality increases with abnormal liver function at higher doses, should not be given to subjects if the total bilirubin is greater than

institutional upper limit of normal (ULN), or if AST and/or ALT is greater than 1.5X ULN concomitant with alkaline phosphatase greater than 2.5X ULN, should not be given if the neutrophil count of the subject is less than 1500 cell/mm³, should not be given if subjects have a history of severe hypersensitivity to docetaxel or drugs formulated with polysorbate 80, and may cause severe fluid retention.[56]

1.4.3 BMS-936558 Clinical Results

Two studies contributed to most of the monotherapy clinical experience with BMS-936558 (nivolumab) in subjects with malignancies. CA209001 was a Phase 1 single-dose dose escalation study in subjects (N = 39) with previously treated advanced or metastatic cancer. Subjects received a single dose of BMS-936558 (nivolumab) at 0.3, 1, 3, or 10mg/kg with an option for re-treatment at 3 months. CA209003 is an ongoing Phase 1 open-label, multiple dose escalation study in subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC (squamous and non-squamous), colorectal cancer, and hormone-refractory prostate cancer. Subjects received BMS-936558 (nivolumab) at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of February 24, 2012, 296 subjects were evaluable for safety (cutoff date February 24, 2012) across the entire dose range, including 122 NSCLC subjects, and 236 were evaluable for efficacy (cutoff date July 1, 2011), including 76 subjects with NSCLC. Updated data included 129 NSCLC subjects from the final CA209003 CSR (March 5, 2013 database lock), with long-term follow-up information based on a 17-Sep-2013 database lock.

1.4.3.1 Clinical Pharmacology Summary

Single dose pharmacokinetics (PK) of BMS-936558 (nivolumab) was evaluated in subjects with multiple tumor types in CA209001, whereas multiple dose PK is being evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ~350 subjects from CA209001, CA209002, and CA209003.

Single dose PK of BMS-936558 (nivolumab) was evaluated in 39 subjects with mutiple tumor types in study CA209001 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of BMS-936558 (nivolumab) is linear in the range of 0.3 to 10 mg/kg with dose- proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (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-HALF of BMS-936558 (nivolumab) is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of BMS-936558 (nivolumab) may be similar to IgG4. Both elimination and distribution of BMS-936558 (nivolumab) appear to be independent of dose in the dose range studied. Additional details are provided in investigator brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from CA209001, CA209002 and CA209003. The body weight normalized dosing

produces approximately constant trough concentrations over a wide range of body weights, and hence is appropriate for future clinical trials of BMS-936558 (nivolumab).

1.4.3.2 Safety Summary

In CA209001, treatment-related AEs were reported for 35 of 39 (89.7%) subjects; 12 subjects (30.8%) had reported treatment-related AEs of Grade 3 or 4. The most frequently reported AEs, regardless of causality, included fatigue (56.4%), nausea (43.6%), proteinuria (38.5%), constipation (33.3%), back pain (33.3%), dry mouth (28.2%), vomiting (28.2%), rash (25.6%) and dyspnea (25.6%). Additional events of interest included diarrhea (8 subjects) and thyroid stimulating hormone increased (7 subjects); none were serious or of high grade. Two subjects reported treatment-related SAEs of hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). There was no dose-related pattern with regard to the incidence, severity, or relationship of AEs. Common laboratory abnormalities (reported in ≥ 10% of subjects) that were considered related to BMS-936558 (nivolumab) included decreases in CD4 counts, lymphopenia, and increases in C-reactive protein. A Grade 4 event of lymphocyte count decreased was reported for 1 subject. Twelve (12) deaths were reported during the course of the study or within 30 days of last dose of study drug, all considered unrelated to BMS-936558 (nivolumab).

No MTD was identified in CA209003 at any dose level. BMS-936558 (nivolumab) related AEs of any grade occurred in 70% of subjects. The most frequent drug-related AEs occurring in ≥ 5% of subjects included fatigue (24%), rash (12%), diarrhea (11%), pruritus (10%), nausea (8%), decreased appetite (8%), hemoglobin decreased (6%) and pyrexia (5%). The majority of events were low grade, with grade 3-4 drug-related AEs observed in 14% of subjects. The most common Grade 3-4 drug-related AEs occurring in ≥ 1% of subjects were fatigue (2%), pneumonitis (1%), hypoxia (1%), diarrhea (1%), colitis (1%), abdominal pain (1%), AST/ALT increased (1% each), blood alkaline phosphatase increased (1%), lipase increased (1%), pneumonia (1%), hypophosphatemia (1%), and lymphopenia (1%). Drug-related serious AEs (SAEs) occurred in 11% of subjects. Grade 3-4 drug-related SAEs occurring in ≥ 1% of subjects were: pneumonitis (1%), pneumonia (1%), lipase increased (1%) and diarrhea (1%). The spectrum, frequency, and severity of BMS-936558 (nivolumab) -related AEs were generally similar across dose levels and histological subtypes.

Drug-related adverse events of special interest (AEOSIs), with potential immune-related etiologies, included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis, among others. Hepatic or gastrointestinal AEOSIs were managed with treatment interruption and administration of corticosteroids, and were generally completely reversible. Endocrine AEOSIs were managed with replacement therapy. Several subjects in these categories successfully reinitiated treatment with BMS-936558 (nivolumab). Drug-related pneumonitis occurred in 3% of subjects; grade 3-4 pneumonitis developed in 3 subjects (1%). No clear relationship between the occurrence of pneumonitis and tumor type, dose level, or the number of doses received was noted. Early grade pneumonitis was generally reversible with treatment discontinuation and corticosteroid administration. In 3 subjects, infliximab and/or mycophenolate were utilized for additional immunosuppression, with unclear effectiveness. There were 3 (1%) drug-related deaths, due to pneumonitis.

Because of the potential for the development of BMS-936558 (nivolumab) -related AEs including AEOSI, management algorithms have been developed for suspected pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, endocrinopathy, and nephrotoxicity, and are contained within the IB.

As of 03-Apr-2013, three subjects out of approximately 1200 patients on nivolumab clinical trials have developed opportunistic infections (2 cases of Aspergillus pneumonia, and 1 case of Pneumocystis jiroveci pneumonia) after receiving prolonged treatment with high dose steroids for nivolumab-related adverse events. Details of these cases are available in the Investigator Brochure.

Because of the potential for opportunistic infections with prolonged high dose corticosteroids administration, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as *Pneumocystis jiroveci* and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients that develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[57] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in BMS-936558 (nivolumab) exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with BMS-936558 (nivolumab) during pregnancy.

Additional details on the safety profile of BMS-936558 (nivolumab), including results from other clinical studies, are also available in the IB.

1.4.3.3 Anti-tumor Activity Summary

Preliminary efficacy data from CA209003 was evaluated as of July 1, 2011, which provided a minimum follow-up of 8 months. Clinical antitumor activity was observed in melanoma, RCC, and NSCLC at all BMS-936558 (nivolumab) doses tested. NSCLC subjects were treated at doses of 1, 3, and 10 mg/kg. Antitumor activity was mainly observed in the 3 and 10 mg/kg dose groups, and exposure-response appeared to be relatively flat at doses ≥ 3 mg/kg. At the 3 and 10 mg/kg dose levels, the RECIST-defined objective response rates for all histologies were 32% and 18%, respectively. The corresponding disease control rates (which included any subject who achieved a best overall response of CR, PR or SD) were 53% and 46%, respectively. PFS rates at 24 weeks were 41%, and 24%, respectively, indicating durable disease control. Differential

activity was observed between squamous versus non-squamous histologies. Substantial activity was noted in the squamous histology subgroup (n=18), where the ORR and DCR in the 3 mg/kg dose group were 50% and 67%, respectively (the ORR for squamous histology subjects across all dose groups was 33%). Responses were durable; as of the cutoff date, the median PFS in the 3 mg/kg squamous group had not been reached, and 3 of 6 subjects had experienced PFS > 6 months. One subject who achieved PR (67% tumor reduction) experienced a response duration of 134 weeks. Activity in NSCLC is especially notable in that the majority of subjects had received 2 or more prior therapies. These preliminary data suggest that BMS-936558 (nivolumab) induces substantial durable disease control in heavily pretreated subjects with NSCLC, and in particular in subjects with squamous histology.

Response data from the final CA209003 CSR (March 5, 2013 database lock) confirmed anti-tumor activity in pretreated NSCLC subjects. Confirmed objective responses were observed in 22/129 NSCLC subjects (ORR 17.1%, CI: 11.0, 24.7) treated at any nivolumab dose level (1, 3, or 10 mg/kg Q2W), with comparable results for both SQ and NSQ histologies. The ORRs in SQ NSCLC subjects were 9/54 (16.7% [95% CI: 7.9, 29.3]) across dose levels, and 4/18 (22.2% [95% CI: 6.4, 47.6]) at the 3 mg/kg dose level. A CSR addendum based on a 17-Sep-2013 database lock provided long-term (minimum 2 years) follow-up indicating durability of responses in the 22 confirmed responders treated with any nivolumab dose. Median DOR in all NSCLC subjects was 17 months (CI: 8.7, NR; range: 1.4+ - 30.8+ months). Milestone PFS rates were 22% (95% CI: 15, 30) at 48 weeks and 9% (95% CI: 4, 15) at 96 weeks, and milestone OS rates were 42% at 48 weeks and 24% at 96 weeks. Effects on PFS and OS were consistent across histologies, and appeared to show a slowing in event rates between the 48-week and 96-week milestones, consistent with sustained clinical effect.

1.5 Overall Risk/Benefit Assessment

Subjects with metastatic squamous cell NSCLC who progress with first-line therapy represent a great unmet need. The clinical activity of BMS-936558 (nivolumab) observed to date in squamous cell NSCLC suggests the potential for improved clinical outcomes as monotherapy. However, the potential benefit over standard of care docetaxel is not yet known. Docetaxel has a well characterized adverse event profile consistent with cytotoxic chemotherapy, including the potential for serious pancytopenia, fluid retention, peripheral neuropathies, asthenia, diarrhea, nausea and vomiting. BMS-936558 (nivolumab) also has the potential for clinically relevant adverse events including liver toxicities, thyroiditis, pneumonitis, and diarrhea. However, the activity and manageable AEs profile observed with BMS-936558 (nivolumab) supports a head-to-head evaluation versus docetaxel in second-line squamous cell NSCLC.

To assure an ongoing favorable benefit-risk assessment for subjects enrolled onto CA209017, an independent Data Monitoring Committee (DMC) will be utilized to monitor the activity and safety of BMS-936558 (nivolumab) versus docetaxel throughout the conduct of the trial.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling, information to be provided to subjects and any updates.

The investigator or sponsor should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

BMS will provide the investigator with an appropriate (ie, Global or Local) sample informed consent form which will include all elements required by ICH, GCP and applicable regulatory requirements. The sample informed consent form will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

Investigators must:

1. Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.
2. Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study
3. Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.
4. Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5. If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the subject.
6. Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the subjects' signed ICF and, in the US, the subjects' signed HIPAA Authorization.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records.

Subjects unable to give their written consent (eg, stroke subjects, or subjects with severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with the subjects' understanding, and should they become capable, personally sign and date the consent form as soon as possible. The explicit wish of a subject unable to give his or her written consent, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

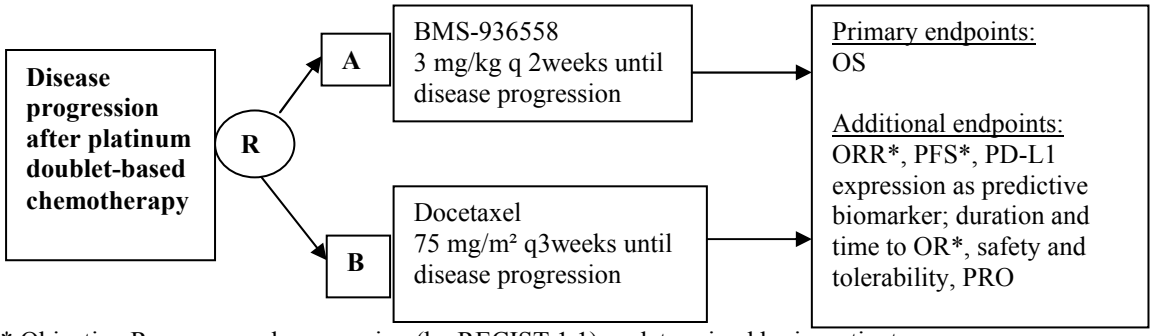
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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 chemotherapy. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be assigned to one of two treatment arms in a 1:1 ratio (see Study Design and Duration in Figure 3.1-1 below). Randomization will be stratified according to the following factors: prior treatment with paclitaxel-based doublet vs. other doublet, and region (US vs. Europe vs. Rest of World).

Figure 3.1-1: Study Design



* Objective Response and progression (by RECIST 1.1) as determined by investigator

Treatment should be initiated within 3 business days of randomization. BMS-936558 (nivolumab) or docetaxel (depending on randomized treatment Arm) will be administered as an IV infusion over 60 minutes on Treatment Day 1. A treatment cycle is defined as 2 weeks for BMS-936558 (nivolumab) and 3 weeks for docetaxel.

This study will consist of 3 phases: screening, treatment, and follow-up.

Screening:

- Begins by establishing subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID.
- Tumor tissue (archival or recent tumor biopsy) must be available and received by the central lab for correlative studies in order for a subject to be randomized. Subjects must consent to allow the acquisition of tumor tissue by study personnel for performance of the correlative studies. (Table 5.1-1)
- Baseline disease or tumor assessments should be performed within 28 days of randomization (according to Table 5.1-1).
- Subject is assessed for study eligibility within the required timeframe found in Table 5.1-1.

Treatment:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to one of the treatment arms. Treatment should begin within 3 business days of randomization.
- All of the laboratories and vital signs will be collected on Day 1 of each cycle, and specific laboratories will be performed more frequently during the first cycle. (according to Table 5.1-2 or Table 5.1-3, depending on the randomized treatment arm) Adverse event assessments should be documented at each clinic visit.
- Biomarker, PK and immunogenicity samples will be done according to the schedules in Section 5.1 (Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-5).
- Patient-reported outcome (PRO) instruments will be completed after randomization, prior to the first dose of study therapy on Day 1, and prior to study procedures and dosing on Day 1 of each visit for which an ePRO instrument assessment is scheduled, according to Table 5.1-2or Table 5.1-3, depending on randomized treatment assignment.
- Study drug is administered as an IV infusion on Treatment Day 1 of each cycle (frequency is dependent on the treatment arm) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 (nivolumab) beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.
- Subjects will be evaluated for response according to the RECIST 1.1 criteria. Radiographic assessments will be obtained in both treatment arms at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 (nivolumab) beyond progression), lost to follow-up, or withdrawal of study consent.
- Baseline and all subsequent scans will be submitted to an independent radiology review committee (IRC) for banking, once the subject is randomized and throughout the study period.
- This phase ends when the subject is discontinued from study therapy. Please refer to Section 3.5 for a complete list of reasons for discontinuation.

Follow-up:

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Subjects will have two follow-up visits for safety within the first 100 days from the last dose of study therapy (X01 = 30 days from the last dose [± 5 days] or coinciding with the date of discontinuation [± 5 days] if date of discontinuation is greater than 35 days after last dose, and X02 = 70 days from X01 [± 5 days]) according to Section 5.3.3 and Table 5.1-4. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, or withdrawal of study consent
- Subjects who discontinue study therapy for reasons other than disease progression will continue to have radiographic assessments every 6 weeks (± 5 days) until disease progression, lost to follow-up, or withdrawal of study consent.

- All subjects will be followed for overall survival every 3 months until death, lost to follow-up, or withdrawal of study consent.
- For subjects randomized to receive BMS-936558 (nivolumab) (Arm A) only, the 2 follow-up visits will include PK and immunogenicity samples according to Table 5.1-5.
- ePRO instruments will be completed at a frequency according to Table 5.1-4 (first two follow-up visits). In addition in the survival phase, the EQ-5D will be assessed every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law.

The final analysis of the overall survival primary endpoint will be conducted after at least 231 subjects have died (approximately 38 months from start of randomization). Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee, or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

For entry into the study, the following criteria MUST be met.

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests and other requirements of the study.

2. Target Population

a) Men and women ≥ 18 years of age

b) 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).

c) Subjects must have experienced disease recurrence or progression during or after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease.

i) Maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy

ii) 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.

iii) 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.

d) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria; Radiographic Tumor Assessment performed within 28 days of randomization

i) Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site

e) Eastern Cooperative Oncology Arm (ECOG) performance status of ≤ 1

f) A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation, as described in Section 5.4.2. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient.

g) All baseline laboratory requirements will be assessed and should be obtained within **-14** days (unless otherwise specified in Table 5.1-1) of randomization. Screening laboratory values must meet the following criteria

i) WBCs ≥ 2000/µL

ii) Neutrophils ≥ 1500/µL

iii) Platelets ≥ 100 x 10^3/µL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine of ≤ 1.5 X ULN or creatinine clearance > 40 mL/minute (using Cockcroft/Gault formula)

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/ dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/ dL}}$$

vi) AST ≤ 1.5X ULN

vii) ALT ≤ 1.5X ULN

viii) Total bilirubin ≤ ULN (except subjects with Gilbert Syndrome who must have total bilirubin <3.0 mg/dL)

h) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to randomization

3. Age and Reproductive Status

a) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 2. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours. Contraception should be continued for a period of at least 30 days plus the time required for the investigational drug to undergo five half lives. For women randomized to receive BMS-936558 (nivolumab), this is equivalent to 23 weeks after discontinuation of treatment. For women randomized to receive docetaxel, this is equivalent to 33 days after discontinuation of treatment

b) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product.

c) Women must not be breastfeeding

d) Men who are sexually active with WOCBP 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. Men that are sexually active with WOCBP must follow instructions for birth control for a period of 90 days plus the time required for the investigational drug to undergo five half lives. For men randomized to receive BMS-936558 (nivolumab), this is equivalent to 31 weeks after discontinuation of treatment. Men randomized to receive docetaxel must follow instructions for birth control as per the SmPC (6 months after discontinuation of treatment), or package insert.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) 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).

b) Subjects with carcinomatous meningitis

2. Medical History and Concurrent Diseases

a) 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.

b) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Corticosteroids with minimal systemic absorption (for example topical, inhalational, or as specified in Section 3.4.3), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

c) 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).

d) Prior treatment on the first-line study CA184104

e) Prior treatment with docetaxel

f) Subjects with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

g) Other active malignancy requiring concurrent intervention

h) 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

i) 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.

j) 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

3. Physical and Laboratory Test Findings

a) Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).

b) Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

4. Allergies and Adverse Drug Reaction

a) History of severe hypersensitivity reactions to other monoclonal antibodies.

b) History of severe hypersensitivity reaction to prior paclitaxel

c) History of allergy or intolerance (unacceptable adverse event) to study drug components or Polysorbate-80-containing infusions.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

b) Women with a positive pregnancy test at enrollment or prior to administration of study medication

6. Prohibited Treatments and/or Restricted Therapies

a) Ongoing or planned administration of anti-cancer therapies other than those specified in this study

b) Use of corticosteroids or other immunosuppressive medications as per Exclusion Criteria 2b

c) Strong CYP3A4 inhibitors (See Section 3.4.1)

d) Treatment with any investigational agent within 14 days of first administration of study treatment

7. Other Exclusion Criteria

a) 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

b) Prisoners or subjects who are involuntarily incarcerated

c) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

3.3.3 Women of Childbearing Potential

A Woman of Childbearing Potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

Women treated with hormone replacement therapy, (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used:

- 1 week minimum for vaginal hormonal products, (rings, creams, gels)
- 4 week minimum for transdermal products
- 8 week minimum for oral products
- Other parenteral products may require washout periods as long as 6 months

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following strong CYP3A4 inhibitors should be avoided for subjects receiving docetaxel during the study. This includes (but is not limited to):

- Ketoconazole
- Itraconazole
- Clarithromycin
- Atazanvir
- Indinavir

- Nefazodone
- Nelfinavir
- Ritonavir
- Saquinavir
- Teithromycin
- Voriconazole

The following are prohibited for all subjects during the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents
- Immunosuppressive doses of systemic corticosteroids (except as stated in this Section 3.4.3).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, surgical resection of lesions, non-palliative radiation therapy, or standard or investigational agents for treatment of NSCLC).

Concomitant palliative and supportive care for disease related symptoms (including bisphosphonates and RANK-L inhibitors) is allowed if initiated prior to first dose of study therapy (prior radiotherapy must have been completed at least 2 weeks prior to randomization per Inclusion criteria 2h). See Section 3.4.3 for guidance on concomitant palliative radiotherapy.

3.4.2 Other Restrictions and Precautions

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. Corticosteroids with minimal systemic absorption (for example topical, inhalational, or as specified in Section 3.4.3), and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

3.4.3 Permitted Therapy

Subjects are permitted the use of topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Adrenal replacement steroid doses > 10 mg daily predinisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.

The potential for overlapping toxicities with radiotherapy and BMS-936658 currently is not known. Therefore, palliative radiotherapy is not recommended while receiving BMS-936558

(nivolumab). If palliative radiotherapy is required, then BMS-936558 (nivolumab) should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs considered related to radiotherapy should resolve to Grade ≤ 1 prior to resuming BMS-936558 (nivolumab). Only non-target bone lesions that do not include lung tissue in the planned radiation field or CNS lesions may receive palliative radiotherapy while on study treatment. Details of palliative radiotherapy should be documented in the source records and electronic case report form (eCRF). Details in the source records should include: dates of treatment, anatomical site, dose administered and fractionation schedule, and adverse events. Subjects requiring palliative radiotherapy should be assessed for disease progression. Subjects considered as having progressive disease are required to discontinue study therapy, or in Arm A, if appropriate, continue BMS-936558 (nivolumab) therapy as treatment beyond progression. Administration of additional BMS-936558 (nivolumab) to subjects who experienced disease progression at the time of palliative radiotherapy should follow guidelines specified in Section 4.3.4 Treatment beyond Disease Progression.

3.5 Discontinuation of Subjects from Treatment

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

- Withdrawal of informed consent (subject's decision to withdraw for any reason)
- 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
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol-specific reasons for discontinuation (See Section 4.3.5**)**

All subjects who discontinue should comply with protocol specified follow-up and survival procedures as outlined in Section 5. The ONLY exception to this requirement is when a **subject withdraws consent** for all study procedures or loses the ability to consent freely (ie, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If a subject was withdrawn before completing the study, the reason for withdrawal must be entered on the appropriate case report form (CRF) page.

3.6 Post Treatment Study Follow Up

In this study Overall Survival is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study.

Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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 the subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow up in writing, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow Up

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of three documented phone calls, faxes or emails as well as lack of response by the subject to one registered mail letter. All attempts should be documented in the subject's medical records. If it is determined that the subject has died, the site will use permissible local methods to obtain the date and causeof death.

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

Study drugs include both Noninvestigational (NIMP) and Investigational Medicinal Products (IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial.
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (eg., backbone therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

4.1 Study Treatments

BMS-936558 (nivolumab) 100 mg (10 mg/mL) will be packaged in an open-label fashion.

Ten BMS-936558 (nivolumab), 10 mL vials will be packaged within a carton (see Table 4.1-1), and are not subject or treatment arm specific. Vial assignments by subject will be made through the IVRS to track usage and resupply.

Subjects will be randomized to one of 2 treatment arms on study: BMS-936558 (nivolumab) at 3 mg/kg, or docetaxel at 75mg/m^2. Treatment should be initiated within 3 business days of randomization. Each subject will be dosed at a frequency according to their treatment Arm assignment until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 (nivolumab) beyond progression), discontinuation due to toxicity, withdrawal of consent, or the study ends.

Table 4.1-1: Product Description - Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 to 8 °C. Protect from light and freezing.
Docetaxel [a] Concentrate for solution for infusion	160 mg (20 mg/mL)[a]	8 mL vial/ Open-label	1 vial per carton / Open-label	Pale yellow to brownish yellow solution	Do not store above 25°C. Store in original package and Protect from light.
Dexamethasone Tablets[b]	4 mg[a]	Wallet (blister) card of 20 tablets / Open-label	N/A	Scored tablets	Store at 15-25° C.

[a] For sites/countries in which investigative site staff will procure locally marketed product of docetaxel and/or dexamethasone, the potency/packaging size may differ based on the locally available product.

[b] Dexamethasone is being provided by Bristol-Myers Squibb to specific countries where required, for the docetaxel arm (premedication).

In countries where local sourcing is allowed, sites may use their local institutional equivalent of dexamethasone.

NOTE: Medications used to treat BMS-936558 (nivolumab)-related infusion reactions are (eg, diphenhydramine, acetaminophen/paracetamol, corticosterioids) considered NIMPs (noninvestigational products) and will not be provided by the sponsor. These will be obtained by the investigational sites as marketed product, which should be stored in accordance to the package insert or summary of product characteristics (SmPC). For further details related to these medications and BMS-936558 (nivolumab)- related infusion reactions, please see Section 4.3.6.

4.1.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently than the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form.

The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations.

In this protocol, investigational product(s) is/are:

- BMS-936558 (nivolumab)
- Docetaxel

Docetaxel will be provided by BMS as listed in Table 4.1-1 for certain countries and may be procured by the investigative sites in other countries as local commercial product, where allowed by local regulations. The sites will also procure IV bags, diluents, and micron in-line filters (ie, 0.2/ 0.22 micron; see current BMS-936558 (nivolumab) Investigator Brochure for required filter details).

4.1.2 Noninvestigational Product

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered as noninvestigational products.

In this protocol, noninvestigational products are:

Dexamethasone (or institutional equivalent) given as premedication for docetaxel, and any medications used to treat BMS-936558 (nivolumab) related infusion reactions (see Section 4.3.6).

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the sponsor. If concerns regarding the quality or appearance of the study drug arise, do not dispense the study drug and contact the sponsor immediately. BMS-936558 (nivolumab) vials must be stored in the refrigerator at 2-8°C, protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton.

Docetaxel and dexamethasone should be stored according to the market product package insert or clinical label.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Recommended safety measures for preparation and handling of BMS-936558 (nivolumab) include laboratory coats and gloves.

After BMS-936558 (nivolumab) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours. For details on prepared drug storage and use time under room temperature/light and refrigeration, please refer to the current BMS-936558 (nivolumab) Investigator Brochure. [20]

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936558 (nivolumab) and polyolefin bags have been observed.

BMS-936558 (nivolumab) is to be administered as a 60 minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline (per institutional standard of care).

Details regarding the mixing and concentrations of the dose (preparation) and administration will be found in the current Investigator brochure for BMS-936558 (nivolumab).[20]

For sites utilizing the docetaxel 160 mg vials provided by Bristol-Myers Squibb, the preparation instructions found within the current SmPC should be followed. [58]

For sites utilizing locally-sourced docetaxel, please follow storage and administration instructions on the package insert or SmPC. [56,58]

4.2 Method of Assigning Subject Identification

After the subject's eligibility is established and informed consent has been obtained, the subject will be enrolled and a number will be assigned through an interactive voice response system (IVRS). Specific instructions and procedures for using IVRS will be provided to the investigational site in a separate document/ manual.

The investigator (or designee) will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date of informed consent
- Date of birth
- Gender at birth

Once enrolled in IVRS, enrolled subjects that have signed informed consent and met all eligibility criteria will be ready to be randomized through the IVRS, upon confirmation of receipt of required tissue sample by the central lab. The following information is required for subject randomization:

- Subject number
- Date of birth
- Gender at birth
- Diagnosis
- Date of informed consent
- Prior paclitaxel vs. other prior treatment
- Region (US/ Canada vs Europe vs Rest of World)

Subjects meeting all eligibility criteria and randomized onto the study will be assigned to one of the two treatment arms, and stratified by the following factors: prior paclitaxel vs. other prior treatment, and region. The randomization will be carried out via permuted blocks within each stratum.

4.2.1 Treatment Arms

Arm A: BMS-936558 (nivolumab)

No premedications are recommended for initiation of dosing.

Arm B: Docetaxel

Premedication with corticosteroids will be given to subjects randomized to the docetaxel treatment Arm. The recommended premedication per the USPI and SmPC is dexamethasone 8mg PO BID given one day before, on the day of, and one day after administration of chemotherapy. For institutions that have established an equivalent premedication regimen consistent with local docetaxel labeling, such premedication regimens will be permitted.

4.3 Selection and Timing of Dose for Each Subject

Subjects randomized to Arm A (the experimental arm) will receive treatment with BMS-936558 (nivolumab) as a 60 minute IV infusion, on Day 1 of a treatment cycle every 2 weeks. Dosing calculations should be based on the body weight assessed as per Table 5.1-2. The dose should remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight. All doses should be rounded to the nearest milligram. There will be no dose escalations or reductions of BMS-936558 (nivolumab) allowed. Subjects may be dosed no less than 12 days from the previous dose. There are no premedications recommended for BMS-936558 (nivolumab) on the first cycle. If an acute infusion reaction is noted, subjects should be managed according to Section 4.3.6.

Subjects randomized to Arm B (the control arm) will receive treatment with docetaxel as a 60 minute IV infusion on Day 1 of a treatment cycle every 3 weeks. Dosing calculations should

be based upon the body surface area calculation assessed as per Table 5.1-3. The dose should remain the same if the subject's weight is within 10% of the baseline weight or prior dose weight. Dose modifications for toxicity will be performed according to Section 4.3.2.2. Subjects may be dosed no less than 19 days from the previous dose.

On both arms, treatment may be delayed for up to a maximum of 6 weeks from the last dose (See Sections 4.3.1 and 4.3.5).

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose delay, reduction, or discontinuation) will be based on specific laboratory and adverse event criteria.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab [and other agents as applicable per protocol] is/are considered an immuno-oncology agent(s) in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological

The above algorithms are found in the BMS-936558 (nivolumab) Investigator Brochure.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event, consider recommendations provided in Section 1.4.3.2.

4.3.1 Dose Delay Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

4.3.1.1 BMS-936558 Dose Delay Criteria

BMS-936558 (nivolumab) administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:

- Grade 3 lymphopenia or leukopenia does not require dose delay
- If a subject has a baseline AST, ALT or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
- If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.1.2 Docetaxel Dose Delay Criteria

Docetaxel administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, neutrophil count, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia does not require dose delay
  - Should not be given if neutrophil counts are < 1500 cells/mm^3
  - Should not be given if total bilirubin > upper limit of normal (ULN), or if AST and/or ALT > 1.5xULN concomitant with alkaline phosphatase > 2.5xULN
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication

Subsequent dose reductions may be required as per Section 4.3.2.2.

Subjects receiving docetaxel may receive growth factors (including G-CSF and erythropoietin) at the discretion of the investigator.

4.3.2 Dose Reductions

4.3.2.1 BMS-936558 Dose Reductions

There will be no dose modifications of BMS-936558 (nivolumab)

4.3.2.2 Docetaxel Dose Reductions

Dose reductions of docetaxel may be required, and will be performed according to Table 4.3.2.2-1

Table 4.3.2.2-1: Dose Reductions of Docetaxel [56]	
Dose Level	**Docetaxel**
Starting dose	75 mg/m^2
First dose reduction	55 mg/m^2
Second dose reduction	37.5 mg/m^2
Third dose reduction	Discontinue docetaxel

Doses of docetaxel will be modified for subjects who experience docetaxel-related events of febrile neutropenia, neutrophils < 500 cell/mm³ for > 7 days, severe or cumulative cutaneous reactions, or other Grade 3/4 non-hematological toxicities during docetaxel treatment. Subjects should have treatment delayed according to Sections 4.3.1.2 and 4.3.3.2, and then resumed at one dose level reduction (55 mg/m^2). Should these AEs occur after the first dose reduction, then a second dose reduction to 37.5 mg/m² is permitted. If a third dose reduction is required, then the subject should discontinue docetaxel treatment and enter the follow-up phase.

Subjects who develop Grade ≥ 3 peripheral neuropathy, or who otherwise meet criteria specified in Section 4.3.5.2, should discontinue docetaxel treatment and enter the follow-up phase.

4.3.3 Criteria to Resume Dosing

4.3.3.1 Criteria to Resume Treatment with BMS-936558

Subjects may resume treatment with BMS-936558 (nivolumab) when the drug-related AE(s) resolve(s) 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, or colitis 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, except as specified in Section 4.3.5.1.

4.3.3.2 Criteria to Resume Treatment with Docetaxel

Subjects may resume treatment with docetaxel when the drug-related AE(s) resolve(s) 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 decreased neutrophil counts, or with elevations in total bilirubin, AST or ALT must meet criteria for resuming treatment according to the boxed warning contained within the docetaxel Prescribing Information
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5.2) should have treatment permanently discontinued

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.2.

When resuming docetaxel treatment, please follow the dose reduction recommendations noted in Section 4.3.2.2.

4.3.4 Treatment Beyond Disease Progression

As described in Section 1.4.3.3, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[59]

Subjects treated with docetaxel (Arm B) will not be permitted to continue their treatment beyond initial RECIST 1.1 defined PD.

Subjects treated with BMS-936558 (nivolumab) (Arm A) will be permitted to continue treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

1. Investigator-assessed clinical benefit, and do not have rapid disease progression
2. Tolerance of study drug
3. Stable performance status
4. Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
5. Subject provides written informed consent prior to receiving additional BMS-936558 (nivolumab) treatment, using an ICF describing any reasonably foreseeable risks or discomforts, or other alternative treatment options.

The decision to continue treatment beyond initial progression should be discussed with the BMS medical Monitor and documented in the study records.

A radiographic assessment/ scan should be performed within six (6) weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically

deteriorating and unlikely to receive any benefit from continued treatment with BMS-936558 (nivolumab)

If the investigator feels that the BMS-936558 (nivolumab) subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on Table 5.1-2.

For the subjects who continue BMS-936558 (nivolumab) study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden volume from time of initial PD. This includes an increase in the sum of all target lesions and/ or the development of new measurable lesions. Treatment should be discontinued permanently upon documentation of further disease progression

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden volume if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm).

For subjects in both treatment arms, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression (ie radiographic confirmation) even after discontinuation of treatment.

4.3.5 Treatment Discontinuation Criteria

Tumor assessments for all subjects should continue as per protocol even if dosing is discontinued.

4.3.5.1 BMS-936558 Dose Discontinuation

BMS-936558 (nivolumab) treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, 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:
    i) Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    ii) Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

(1) AST or ALT > 5-10x ULN for > 2 weeks

(2) AST or ALT > 10x ULN

(3) Total bilirubin > 5x ULN

(4) 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 BMS-936558 (nivolumab)dosing

4.3.5.2 Docetaxel Dose Discontinuation

Docetaxel treatment should be permanently discontinued for the following:

- Any Grade ≥ 3 peripheral neuropathy
- Any Grade 3 non-skin drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities:
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    i) Grade 3 drug-related thrombocytopenia associated with bleeding requires discontinuation
    ii) Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      (1) AST or ALT > 5-10x ULN for > 2 weeks
      (2) AST or ALT > 10x ULN
      (3) Total bilirubin > 5x ULN

(4) 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:
  - Grade 4 neutropenia > 7 days despite 2 prior docetaxel reductions requires discontinuation
  - Grade 4 lymphopenia or leukopenia does not require discontinuation
  - 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 do not require discontinuation
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - 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 docetaxel dosing

4.3.6 Treatment of BMS-936558-Related Infusion Reactions

Since BMS-936558 (nivolumab) contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines, as appropriate:

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated).

- 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 BMS-936558 (nivolumab) administrations.

For 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).

- Stop the BMS-936558 (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 BMS-936558 (nivolumab) will be administered at that visit.
- 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 BMS-936558 (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).

- Immediately discontinue infusion of BMS-936558 (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. BMS-936558 (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.

In case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine or corticosteroids).

4.4 Blinding/Unblinding

Not applicable.

An open-label (rather than blinded) study design was selected because the management of similar AEs will differ between treatment arms, given the different mechanisms of action of

docetaxel and BMS-936558 (nivolumab). Different dose modification rules (no dose reductions for BMS 936558 vs allowance for dose reductions for docetaxel) and different drug-drug interaction profiles add complexity to any blinding strategy.

Subjects have potentially different AEs, as BMS-936558 (nivolumab) has shown immune-related events while docetaxel has an adverse event profile that consists primarily of hematologic events. Although both drugs have been noted to cause pulmonary AEs, these events are treated differently. With docetaxel, pulmonary AEs are mainly due to neutropenic fever and pneumonia, requiring broad-spectrum antibiotics and growth factors. With BMS-936558 (nivolumab), pulmonary AEs are immune related and are treated with systemic steroids. If this trial is blinded, the management of AEs would potentially be delayed or detrimental to the subject.

4.5 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible BMS Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxics or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met, the responsible BMS Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local,

and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.6.2 Return of Study Drug

If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible BMS Study Monitor.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

4.7 Retained Samples for Bioavailability/Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments and Procedures (CA209017) For ARMS A and B

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed prior to randomization
Medical History	X	
Safety Assessments		
Vital Signs and Oxygen saturation	X	Temperature, BP, HR, RR, O_2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) Obtain vital signs at screening visit and within 72 hours of first dose
Physical Measurements (including Performance Status)	X	Includes Height and Weight, and ECOG status Focused physical exam may be performed at screening, if clinically indicated
Laboratory Tests	X	Labs performed locally within 14 days prior to randomization (unless otherwise specified): CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH Hepatitis B surface antigen (HBV sAg) within 28 days prior to randomization Hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) within 28 days prior to randomization TSH, free T3, free T4 (within 28 days prior to randomization)
Pregnancy Test	X	Performed within **24** hours of randomization (serum or urine for WOCBP only)
Assessment (of signs and symptoms)	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of study randomization, prior to study treatment initiation.
Concomitant Medication collection	X	Within 14 days of randomization

Table 5.1-1: Screening Assessments and Procedures (CA209017) For ARMS A and B		
Procedure	**Screening Visit**	**Notes**
Efficacy Assessments		
Radiographic Tumor Assessment (Chest, abdomen, pelvis)	X	Should be performed within 28 days prior to randomization. MRI of brain (with contrast, unless contraindicated) is required in subjects with a known history of treated brain metastases. Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit.
Biomarker Assessments		
Archived Tumor Tissue or Recent Tumor Biopsy (for IHC)	X	May be archival or recent sample. 1 formalin-fixed paraffin embedded tumor tissue block, or minimum of 10 FFPE unstained slides are needed. Specimens must be received by the central lab prior to subject randomization
Pharmacogenetic Sample (PGx)- Optional	X	Can be obtained at any time after Study and PGx Informed Consent is obtained.

Table 5.1-2: On-Study Assessments ARM A (BMS-936558- nivolumab)						
Procedure	**C1D1**	**C1D8**	**Each cycle (Every 2 weeks) on Day 1(± 3 days)**	**Every Other Cycle (every 4 weeks) on Day 1 (± 3 days)**	**Every 3 cycles (6 weeks ± 3 days)**	**Notes**
Safety Assessments						
Vital Signs and Oxygen saturation	X	X	X			Within 72 hours prior to dosing: Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------continuously----------					Assessed using NCI CTCAE v. 4.0
Physical measurements (including Performance Status)	X	X	X			Includes Weight and ECOG status
Complete blood counts(CBCs) (Results obtained prior to dosing on infusion days)	X	X	X			Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests (Results obtained prior to dosing on infusion days)	X	X	X			Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: Serum chemistry (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), LDH

Table 5.1-2: On-Study Assessments ARM A (BMS-936558- nivolumab)

Procedure	C1D1	C1D8	Each cycle (Every 2 weeks) on Day 1(± 3 days)	Every Other Cycle (every 4 weeks) on Day 1 (± 3 days)	Every 3 cycles (6 weeks ± 3 days)	Notes
Liver Function Testing (Results obtained prior to dosing on infusion days)	X	X	X			Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin
Thyroid Function Testing	X				X	Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. TSH (reflex to free T3 and free T4 if abnormal TSH result)
Review of Concomitant Medications	X	X	X			Review at every visit
Pregnancy Test					X	Serum or urine (for WOCBP only) test to be performed every 6 weeks or more frequently as per local standards

Table 5.1-2: On-Study Assessments ARM A (BMS-936558- nivolumab)						
Procedure	**C1D1**	**C1D8**	**Each cycle (Every 2 weeks) on Day 1(± 3 days)**	**Every Other Cycle (every 4 weeks) on Day 1 (± 3 days)**	**Every 3 cycles (6 weeks ± 3 days)**	**Notes**
Efficacy Assessments						
Radiographic Tumor Assessment					X	Tumor assessments are conducted at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days), from randomization until documented disease progression (discontinuation of study therapy in subjects receiving BMS-936558 (nivolumab) beyond progression). Assessments should include chest and abdomen (with contrast, unless contraindicated) as well as any area that is being monitored. Follow RECIST 1.1 criteria. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated
Biomarker						
Serum (for soluble factors and miRNA Analyses)	X				X*	Must be obtained any time after randomization, prior to dosing C1D1 *In addition, ONE on -study serum sample will be obtained at C4D1 ONLY
PBMC	X		X*		X*	First Sample Must be obtained any time after randomization prior to dosing C1D1 * TWO on study samples will be obtained at C2D1and C4D1 ONLY

Table 5.1-2: On-Study Assessments ARM A (BMS-936558- nivolumab)						
Procedure	**C1D1**	**C1D8**	**Each cycle (Every 2 weeks) on Day 1(± 3 days)**	**Every Other Cycle (every 4 weeks) on Day 1 (± 3 days)**	**Every 3 cycles (6 weeks ± 3 days)**	**Notes**
Peripheral Blood RNA	X		X*		X*	First Sample Must be obtained any time after randomization prior to dosing C1D1 * TWO on study samples will be obtained at C2D1 and C4D1 ONLY
Whole Blood (for SNP testing)	X					Can be obtained on Day -3 to Day 1 prior to dosing
Pharmacokinetic and Immunogenicity Assessments (BMS-936558 Treatment Arm ONLY)	----------throughout study ----------					For detailed sample timing, see Table 5.1-5 in this Section 5.1
Patient reported outcomes (PRO) Assessment	X			X		**For C1D1**- performed after randomization PRIOR to first dose (day -3 to +1). **For on study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. Assessments will be performed at every other cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the t**reatment period**
Health Resource Utilization			X			Except cycle 1. To include: concomitant medication collection
Clinical Drug Supplies						
BMS-936558- nivolumab * (3 mg/kg)	X		X			Record Study Drug Infusion start and stop times. * Subjects may be dosed no less than 12 days from previous dose

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8	Each Cycle every 3 weeks on Day1 (± 3 days)	Every 2 cycles (6 weeks ± 3 days)	Notes
Safety Assessments					
Vital Signs and Oxygen saturation	X	X	X		Within 72 hours prior to dosing: Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable) prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Physical measurements (including Performance Status)	X	X	X		Includes weight (calculated BSA) and ECOG status
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	----------continuously----------				Assessed using NCI CTCAE v. 4.0
Complete blood counts(CBCs) (Results obtained prior to dosing on infusion days)	X	X	X		Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count
Serum Chemistry Tests (Results obtained prior to dosing on infusion days)	X	X	X		Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: Serum creatinine, blood urea nitrogen or serum urea level, sodium, calcium, magnesium, phosphate, potassium, chloride and glucose, LDH
Liver Function Testing (Results obtained prior to dosing on infusion days)	X	X	X		Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. For C2D1 and beyond, to be performed within 72 hours prior to dosing, tests include: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, albumin

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8	Each Cycle every 3 weeks on Day1 (± 3 days)	Every 2 cycles (6 weeks ± 3 days)	Notes
Thyroid Function Testing	X			X	Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated. TSH (reflex to free T3 and free T4 if abnormal TSH result)
Review of Concomitant Medications	X	X	X		Review at every visit
Pregnancy Test				X	Serum or urine (for WOCBP only) test to be performed every 6 weeks or more frequently as per local standard
Efficacy Assessments					
Radiographic Tumor Assessment				X	Tumor assessments are conducted at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days), from randomization until documented disease progression or treatment discontinuation, whichever occurs later. Assessments should include chest and abdomen (with contrast, unless contraindicated) as well as any area that is being monitored. Follow RECIST 1.1 criteria. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated
Biomarker					
Serum (for soluble factors and miRNA Analyses)	X			X	Must be obtained any time after randomization, prior to dosing C1D1 In addition, ONE on -study serum sample will be obtained at C3D1 ONLY
PBMC	X		X*	X*	First Sample Must be obtained any time after randomization prior to dosing C1D1 * TWO on study samples will be obtained at C2D1 and C3D1 ONLY

Table 5.1-3: On-Study Assessments ARM B (DOCETAXEL)

Procedure	C1D1	C1D8	Each Cycle every 3 weeks on Day1 (± 3 days)	Every 2 cycles (6 weeks ± 3 days)	Notes
Peripheral Blood RNA	X		X*	X*	First Sample Must be obtained any time after randomization prior to dosing C1D1 * TWO on study samples will be obtained at C2D1 and C3D1 ONLY
Whole Blood (for SNP testing)	X				Can be obtained on Day -3 to Day 1 prior to dosing
Patient reported outcomes (PRO) Assessment	X		X		**For C1D1**- performed after randomization PRIOR to first dose (day -3 to +1). **For on-study visits**: Assessments (LCSS and EQ-5D) will be performed PRIOR to any study procedures and treatment. Assessments will be performed at every cycle on Day 1 for the first 6 months on study, then every 6 weeks thereafter for the remainder of the treatment period.
Health Resource Utilization			X		Except cycle 1. To include: concomitant medication collection
Clinical Drug Supplies					
Docetaxel (75 mg/m^2) *	X		X		Record Study Drug Infusion start and stop times. Dexamethasone 8mg PO BID (or institutional equivalent) on the day before, day of, and day after chemotherapy. Please use the institutional standard for dexamethasone dosing. *Subjects may be dosed no less than 19 days from the previous dose

Table 5.1-4: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose or coinciding with the date of discontinuation (±5 days) if date of discontinuation is greater than 35 days after last dose X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
Radiographic Tumor Assessment	X*	X	For subjects who discontinue study treatment for reasons other than PD, follow up scans should be performed every 6 weeks (± 5 days) until PD, withdrawal of consent, death, lost to follow-up, *Radiographic assessments for subjects who have not experienced PD ***must*** be obtained every 6 weeks (±5 days), and ***not*** delayed until X01 or X02.
Pharmacokinetic Assessments (BMS-936558 Arm ONLY)	X		For detailed sample timing, see Table 5.1-5 in this Section 5.1
Immunogenicity (BMS-936558 Arm ONLY)	X		
Patient reported outcomes Assessment (PRO)	X	X	Beyond 100 days from the last dose of study therapy, the EQ-5D will be administered every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law.

Table 5.1-4: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose or coinciding with the date of discontinuation (±5 days) if date of discontinuation is greater than 35 days after last dose X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
Safety Assessments			
Vital Signs	X		
Physical Measurements (including Performance Status)	X		
Adverse Events (AE) and Serious Adverse Event (SAE) Assessment	X	X*	*Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, withdrawal of study consent,
Laboratory Tests	X		CBC with differential, Serum chemistry (BUN or serum urea level, serum creatinine, albumin, sodium, potassium, calcium, magnesium, phosphate, chloride), AST, ALT, total bilirubin, alkaline phosphatase, glucose, LDH, TSH (reflex to free T3 and free T4 if abnormal result)
Pregnancy Testing	X		
Review of Concomitant Medications	X		

Table 5.1-4: Follow-up and Survival Procedures (CA209017) For ARM A and B

Procedure	Initial Follow-Up Phase (100 days from date of last study treatment) Follow-up Visits 1 (X01) and 2 (X02) X01 to occur approximately 30 days (±5 days) after last dose or coinciding with the date of discontinuation (±5 days) if date of discontinuation is greater than 35 days after last dose X02 to occur approximately 70 days (±5 days) after X01.	Further Follow-up Phase (beyond X02)	Notes
Collection of Survival Information	X	X	Every 3 months until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.

Table 5.1-5: Pharmacokinetic and Immunogenicity Sample Collection from BMS-936558 (nivolumab) Arm				
Study Day[a]	**Sampling Event (Relative To Time of Infusion) Hour**	**Time (Relative To Start of Infusion) Hour: Min**	**Pharmacokinetic Blood Sample Schedule**	**Immunogenicity Blood Sample Schedule**
C1D1	0 (Predose)	00:00	X	X
C1D1	1.0 (EOI)[b]	01:00	X	
C2D1	0 (Predose)	00:00	X	X
C3D1	0 (Predose)	00:00	X	X
C8D1	0 (Predose)	00:00	X	X
C8D1	1.0 (EOI)[b]	01:00	X	
Every 8th Cycle after C8D1 until discontinuation of study treatment	0 (Predose)	00:00	X	X
First 2 Follow-up visits- (up to 100 days from end of treatment visit- EXCEPT for subjects that WITHDRAW CONSENT)			X	X

[a] If a subject permanently discontinues study drug treatment during the sampling period, they will move to sampling at the follow up visits.

[b] EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration of 1 hour, the collection of this sample should also be delayed accordingly.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigational Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including PKs, biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system (randomization)
- Serious Adverse Event (or eSAE) case report forms
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide

- IRC manual
- ePRO manual

Each site will be provided with a touch screen electronic PC tablet for the subject's completion of the PRO questionnaires. Subjects will enter the data directly on to the electronic PC tablet at the time of the scheduled visits, prior to any study procedures and study drug infusion. There will not be any other source data or data entry for these questionnaires outside of what is on the tablet. The data will then be transferred to the ePRO vendor at specified time points throughout the study. During the survival follow-up period beyond X02, the EQ-5D PRO will be administered at a frequency of every 3 months for the first 12 months, then every 6 months thereafter, as permitted by local law. (see schedule Table 5.1-2, Table 5.1-3 and Table 5.1-4 for frequency of assessments)

5.3 Safety Assessments

5.3.1 Screening Assessments

Screening assessments and procedures must be completed within 28 days of randomization, in accordance with Table 5.1-1

- A complete medical history and concomitant medications
- Assessment of pretreatment signs and symptoms
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours of dosing
- Physical measurements including height, and weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status. Focused physical examination may be performed as clinically indicated.
- Laboratory tests include (performed within 14 days prior to randomization, unless otherwise specified):
  - Blood for complete blood count (CBC) with differential, including neutrophil and lymphocyte count
  - Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, LDH)
  - AST, ALT, total bilirubin, alkaline phosphatase, albumin
  - TSH, free T3 and free T4 (within 28 days prior to randomization)
  - Hepatitis B surface antigen (HBV sAg) and Hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA) - within 28 days prior to randomization
- A pregnancy test for WOCBP will be collected within **24** hours prior to randomization

Signs and symptoms present within 14 days prior to randomization (regardless of relationship to disease) will be recorded. Additionally, record any concomitant medications taken within 14 days of randomization.

5.3.2 On-Study Safety Assessments and Procedures

The following assessments will be monitored according to the frequency for each treatment Arm starting on Cycle 1 Day 1 and will continue at the specified frequency until discontinuation from the study. (See Table 5.1-2 and Table 5.1-3 for frequency of testing by treatment arm)

- Patient reported outcomes Assessments (PRO): Lung Symptom Cancer Scale (LCSS) and EuroPRO Group's EQ-5D
- Vital signs including temperature, blood pressure, heart rate, respiratory rate, oxygen saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to 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 (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 managment algorithm contained within the Investigator's Brochure.
- AEs and SAEs continuously throughout the study
- Physical measurements including weight (and calculated BSA for subjects randomized to treatment Arm B) and ECOG performance status
- CBCs with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count (results to be obtained within 72 hours prior to dosing on infusion days) Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated.
- Serum chemistry tests (BUN or serum urea level, serum creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, LDH). Results to be obtained within 72 hours prior to dosing on infusion days. Screening labs performed within 7 days of C1D1 visit do not need to be repeated unless clinically indicated.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin (results obtained within 72 hours prior to dosing on infusion days). Screening labs performed within 7 days of C1D1 visit do not need to be repeated on C1D1, unless clinically indicated.
- Thyroid function testing includes TSH (reflex to free T3 and free T4 if abnormal TSH result). Screening labs performed within 7 days of C1D1 visit do not need to be repeated on C1D1, unless clinically indicated.
- A pregnancy test for WOCBP will be performed every 6 weeks (or more frequently as per local standard) on study.

Concomitant medications taken throughout the study duration should be recorded within the eCRF.

Blood samples will also be collected for pharmacokinetics and immunogenicity as noted in Table 5.1-5 (for subjects randomized to the BMS-936558 nivolumab treatment Arm A only), and for SNP testing as noted in Table 5.1-2 and Table 5.1-3.

Additionally, serum samples (for soluble factors and miRNA analyses) will be obtained from all randomized subjects prior to first dose of study drug, and during the study at Cycle 4, Day 1 (for the BMS-936558 nivolumab arm) or at Cycle 3, Day 1 (for the docetaxel arm). (See Table 5.1-2 or Table 5.1-3) PBMCs and peripheral blood RNA samples will be collected.

For subjects who discontinue study treatment due to toxicity, please follow the procedures for the last scheduled visit on study treatment (prior to discontinuation of study therapy and follow-up visits) from either Table 5.1-2 or Table 5.1-3 (and Table 5.1-5 -pharmacokinetic and immunogenicity samples for subjects randomized to BMS-936558 nivolumab treatment Arm A only).

5.3.3 Follow-up and Survival Procedures

Subjects will be monitored for safety according to Table 5.1-4. During the 100 days after the last dose of study treatment, subjects will have two follow-up visits for safety. Safety assessments will include: review of concomitant medications, physical measurements, vital signs, ECOG performance status, laboratory measurements (CBC, serum chemistry, liver function and thyroid function), and assessment of signs and symptoms including AEs and SAEs. Beyond 100 days from the last dose of study treatment, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline or deemed irreversible, or until lost to follow-up, or withdrawal of study consent.

Blood samples will be collected for pharmacokinetics and immunogenicity as noted in Table 5.1-5 (only for subjects randomized to BMS-936558 (nivolumab)-at the first 2 follow-up visits up to 100 days from the end of treatment, except for subjects that withdraw consent).

Patient reported outcome (PRO) assessments (LCSS and EQ-5D) will be administered at the first two follow-up visits prior to any study related procedures and dosing. Beyond the 100 days after discontinuation, the EQ-5D will be administered once every 3 months for the first 12 months, then once every 6 months thereafter, as permitted by local law. Each site will be provided with a touch screen electronic PC tablet for the subject's responses of the EQ-5D PRO assessment. Subjects will either enter the data directly on to the electronic PC tablet at the time of an office visits (direct contact) or will respond to the script version of the PRO assessment via telephone contact. If the responses are given by telephone, site personnel will enter the responses onto the PC tablet. The PRO data collection will be according to Table 5.1-4 until death, withdrawal of study consent, or lost to follow-up.

The data will then be transferred to the PRO vendor at time points throughout the study. (see schedule Table 5.1-2, Table 5.1-3and Table 5.1-4for frequency of assessments throughout the study.)

A pregnancy test for WOCBP will be performed during the first two follow-up visits (or more frequently as per local standard).

Beyond the second follow-up visit, subjects should be followed for survival assessment every 3 months until death, lost to follow-up, or withdrawal of consent. The survival assessments may be performed by phone contact or an office visit.

5.4 Efficacy Assessments

5.4.1 Screening (Baseline visit) and On-Study Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1-1, Table 5.1-2, and Table 5.1-3, according to RECIST 1.1 [60]. High resolution CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible, or use the alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 28 days of randomization. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and assessment is required during screening in subjects with a known history of treated brain metastases. All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method according to RECIST 1.1 should be used when recording data, and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound are not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.

Radiographic tumor assessments will be conducted at Week 9 (± 5 days) and every 6 weeks from Week 9 (± 5 days) until disease progression (or until discontinuation of study therapy in patients receiving BMS-936558 (nivolumab) beyond progression), lost to follow-up, or withdrawal of study consent. Tumor assessments for all subjects should continue as per protocol even if dosing is interrupted. Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions will be assessed by the investigator using RECIST 1.1 (see Appendix 1 for details of RECIST 1.1).[60] All radiographic assessments performed for study purposes will be submitted and archived for potential future analyses (eg IRC assessment of imaging-based endpoints).

5.4.2 Screening tumor tissue for PD-L1 Biomarker Analysis (archival or recent biopsy)

A formalin-fixed, paraffin-embedded tumor tissue block or unstained slides–of tumor sample (archival or recent) for biomarker evaulation must be available at screening for all subjects at study entry, and received by the central lab prior to subject randomization. In the case of unstained slides, a minimum of 10 slides are necessary to conduct the planned biomarker analyses. (Biopsies should be of reasonably sufficient size to ensure an adequate amount of tissue for analysis and should be excisional, incisional or core needle; fine needle aspiration is

insufficient). If a recent biopsy has been collected and submitted, submission of archival tissue, if available, is still highly encouraged. In cases where retrospective H&E staining by the central lab determines insufficient tumor tissue is present for biomarker analyses, additional archived tissue may be requested by the sponsor, if available. Complete instructions on the collection, processing, handling, and shipment of all samples, including archival and fresh tumor biopsies, will be provided in a separate procedure manual.

A reference laboratory will receive the samples for immunohistochemistry (IHC) - based analyses aimed at determining the abundance of immunoregulatory proteins including PD-L1. The abundance of PD-L1 protein expression will be correlated with clinical efficacy endpoints. Additional exploratory analyses will be conducted as per Section 5.8.2.

5.4.3 Follow-up and Survival Procedures

Subjects who discontinue study treatment prior to progression, and subjects being treated beyond disease progression, will be followed with radiographic tumor assessments every 6 weeks (± 5 days) until documented or further disease progression, withdrawal of study consent, or subjects are lost to follow-up. Radiographic assessments should be performed according to Section 5.4.1. All radiographic assessments performed for study purposes during the follow-up phase will be submitted and archived for potential future analyses.

Survival will be followed after progression, either by direct contact (office visits) or via telephone contact, according to Table 5.1-4 until death, withdrawal of study consent, or lost to follow-up.

5.4.4 Primary Efficacy Assessment

The primary endpoint of this study is OS. Every effort will be made to collect survival data on all subjects including subjects withdrawn from treatment for any reason, who are eligible to participate in the study and who have not withdrawn consent for survival data collection. If the death of a subject is not reported, all dates in this study representing a date of subject contact will be used in determination of the subject's last known date alive.

5.4.5 Secondary Efficacy Assessments

For secondary efficacy analyses (ORR and PFS as assessed by the investigator, association between PD-L1 expression and efficacy, response duration, and time to response), all subjects will be monitored by radiographic assessment on an every-6-week schedule [beginning from the first on-study assessment on week 9 (±5 days)], to determine changes in tumor size according to Section 5.4.1. RECIST 1.1 criteria will be used for the assessment (see Appendix 1). Subjects achieving a timepoint response of CR or PR will require confirmation for BOR determination as per RECIST 1.1, according to the protocol defined tumor assessment schedule. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks (± 5 days). Additional data to determine the change in proportion of disease-related symptoms in subjects with NSCLC will be collected using LCSS.

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn only from study subjects randomized to the BMS-936558 (nivolumab) treatment arm at the time points indicated in Table 5.1-5. Blood samples should be drawn from a site other than the infusion site on days of infusion. All samples collected pre-dose should be taken just prior to the administration (predose) and end-of-infusion (EOI) samples should be taken just prior to EOI (preferably within 2 minutes prior to EOI) from the contralateral arm (ie, the arm not used for the infusion). If the infusion is interrupted, the reason for interruption will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Serum samples will be analyzed for BMS-936558 (nivolumab) by a validated immunoassay. Additional exploratory analyses may be conducted: exploratory results will not be reported. Further details on pharmacokinetic sample collection and processing will be provided to the site in a procedure manual.

5.6 Biomarker Assessments

Please refer to Section 5.8.2 and 8.4.5 for biomarker assessments and analyses. For the Pharmacogenetic information, please refer to the Pharmacogenetic Amendment 01, as applicable.

5.7 Outcomes Research Assessments

Patient reported outcomes (PRO) will be measured according to Table 5.1-2, Table 5.1-3, and Table 5.1-4, using the following two validated subject self-reported questionnaires: Lung Cancer Symptom Scale (LCSS), and EuroQOL Group's EQ-5D.

Subjects will be asked to complete questionnaires before any clinical activities are performed during visits to the study clinics at on-study visits, and at the designated study visits in the follow-up (post-treatment) phase of the study.

Questionnaires will be provided in the subject's preferred language.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analysis of BMS-936558 (nivolumab) will be collected according to the schedule given in Table 5.1-5. Samples collected from subjects in the nivolumab treatment Arm A will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab by validated immunoassays. Additional characterization (Neutralizing antibodies) for any detected ADA may also be performed using a validated bioassay).

Selected immunogenicity samples also may be analyzed for exploratory analyses; exploratory results will not be reported.

Additionally, serum samples designated for PK or biomarker assessments may also be used for immunogenicity analysis, if required (eg, insufficient volume to complete immunogenicity assessment or to follow up on suspected immunogenicity -related AE).

5.8.2 Exploratory Biomarker Assessments

A variety of factors that could potentially predict clinical response to BMS-936558 (nivolumab) will be investigated in tumor specimens obtained at screening, and in peripheral blood taken both at screening (prior to first dose of study drug) and during the study, from all randomized subjects as outlined in Table 5.1-1, Table 5.1-2 and Table 5.1-3. Data from these investigations will be evaluated for associations with objective response, survival (OS, PFS), and/or safety (adverse event) data. Comparative analyses of markers between the two treatment arms will be used to identify biomarkers with predictive versus prognostic value. Complete instructions on the collection, processing, handling, and shipment of all samples described herein will be provided in a separate procedure manual.

5.8.2.1 Peripheral Blood Markers

Serum-Soluble Factors:

Serum will be obtained from all randomized subjects prior to first dose of study drug, and during the study at Cycle 4, Day 1 (for the BMS-936558 (nivolumab) arm) or at Cycle 3, Day 1 (for the docetaxel arm). To understand the prevalence of circulating proteins and the impact they may have on the clinical activity of BMS-936558 (nivolumab), the protein concentrations of a panel of cytokines, chemokines, and other relevant immunomodulatory, serum-soluble factors will be investigated by ELISA, seromics, and/or other relevant multiplex-based protein assay methods. Analyses may focus also on factors associated with NSCLC prognosis and/or responses to standard chemotherapeutic agents. Examples of analytes to be assessed include but are not limited to factors induced by IFNγ signaling (eg T cell chemoattractants CXCL9; CXCL10), antibodies to tumor-associated antigens, and soluble PD-L1 (sPD-L1), which may play an important role in immune tolerance and disease progression.

Serum miRNA:

MicroRNAs are broadly-expressed, small RNAs that regulate the abundance of mRNA transcripts and their translation into protein. Global miRNA expression profiling has become increasingly common in cancer research, and miRNA signatures that are correlated to stage of disease or to clinical outcomes are now available for a variety of cancer types. Expression profiling of miRNA may be useful also in identifying molecular markers for the prediction of drug-responses and for prospective stratification. Intriguingly, miRNAs are stable in serum and may represent miRNAs over-expressed in tumors and/or reflect immune system activity. Serum taken at baseline and during the study (as indicated in the subsection above) from subjects randomized to each treatment arm will be analyzed for miRNA content by microarray and/or by similar methodologies (eg quantitative RT-PCR). The resulting miRNA expression profiles will be evaluated for associations with response and survival data. Pharmacodynamic changes in miRNA expression also may be monitored. Of particular interest will be the expression of miRNAs that have been implicated in the regulation of genes involved in PD-1 signaling (eg miR-513, which has been shown to regulate PD-L1 and to act as part of an IFNγ-induced signaling cascade) and how the expression of such miRNAs correlate with the expression of immunoregulatory proteins within tumors. Ultimately, this approach may lead to the

identification of unique miRNA signatures that could be useful for identifying NSCLC subjects who are likely (or unlikely) to respond to BMS-936558 (nivolumab) treatment.

Whole Blood SNP:

Whole Blood SNP: Whole blood will be collected from all subjects at C1D1 (can be obtained on Day -3 to Day 1 prior to dosing) to generate genomic DNA for candidate-based and/or whole-genome Single Nucleotide Polymorphism (SNP) analyses. Candidate-based analyses will focus on SNPs within genes associated with PD1 and other immunoregulatory signaling pathways to determine if natural variation within those genes is associated with response to BMS-936558 (nivolumab) and/or with adverse events during treatment. A similar approach will be taken with putative genome-wide association studies (GWAS). Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically-relevant biomarkers identified by other methodologies described in this section.

Peripheral Blood Mononuclear Cells (PBMC)

Immunological monitoring of patients treated with immunotherapeutic agents, such as nivolumab and ipilimumab, has provided insights into the mechanism of action of such agents on immune cells both within the periphery as well as the tumor microenvironment. To characterize the immunomodulatory properties of such agents and to identify candidate predictors of benefit or toxicity, peripheral blood samples have been collected and analyzed to measure the frequency of specific populations of immune cells as well as expression of markers of interest on these cells. In clinical studies of ipilimumab, associations have been reported between benefit and increases of, for example, absolute lymphocyte count, CD8+ cells, Th17 cells, or CD4+ICOShigh T cells.[61] Corresponding data for nivolumab are limited to phase 1 studies, largely in melanoma and RCC patients (unpublished).

To understand the relationship between nivolumab treatment, benefit and immunologic endpoints in NSCLC patients, PBMC specimens will be collected at baseline and on-treatment and evaluated using flow cytometry and other methods. These analyses will be performed to quantify increases or decreases from baseline in various immune cell populations, including but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen specific T cell proliferation or activation pending emerging information from other nivolumab studies.

Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Table 5.1-1, Table 5.1-2, Table 5.1-3 for additional details on the blood sample collection schedule) for PBMC preparation. Samples must be shipped within 48 hours to a BMS-designated central laboratory for processing.

Peripheral Blood RNA

Gene expression analyses of RNA derived from whole blood may provide information on the broad effects of nivolumab immune modulation. Transcriptional profiling of tumors [62] and of whole blood (unpublished) has been conducted within clinical studies of ipilimumab and identified genes that are differentially expressed upon ipilimumab treatment or whose expression

is associated with benefit. To determine whether these or other genes are similarly associated with nivolumab treatment or clinical outcome, genomic expression patterns of whole blood collected at baseline and during on-study treatment will be analyzed (see Table 5.1-1, Table 5.1-2, Table 5.1-3 for additional details on the blood sample collection schedule). Gene expression may be assessed by Affymetrix microarray profiling, qRT-PCR or other technology, with an emphasis on genes with relevant immune function.

5.8.2.2 Tumor Markers

A formalin-fixed, paraffin-embedded tumor tissue (FFPET) block or unstained slides (minimum 10 requested) of tumor sample (archival or recent) for biomarker evaluation will be obtained prior to subject randomization as outlined in Section 5.4.2. A reference laboratory will receive the samples for immunohistochemistry (IHC)-based analyses aimed at determining the abundance of the immunoregulatory proteins such as PD-1, PD-L1 and PD-L2. Additional immunohistochemical analyses may be completed to determine the abundance of other protein markers associated with TILS or with NSCLC disease progression. The abundance of each protein monitored (or combinations of proteins) will be correlated with clinical endpoints.

FFPET may be evaluated also by fluorescent in-situ hybridization (FISH), genetic mutation detection methods, and/or by RT-QPCR as part of additional exploratory analyses of putative biomarkers thought to be associated with response or resistance to therapeutics used in the treatment of NSCLC. Such analyses will be completed retrospectively and within the scope of informed consent.

5.8.3 Healthcare Resource Utilization

Healthcare resource utilization data associated with hospitalizations and non-protocol specified medical visits related to either study therapy or disease will be collected for all randomized subjects. The healthcare resource utilization will be assessed during the study according to treatment arm assignments below:

- Treatment arm A (BMS-936558; nivolumab): Day 1 of cycle 3 and subsequently on Day 1 of every other cycle (every 4 weeks) on study treatment, and at the first 2 follow-up visits after discontinuation of study treatment.
- Treatment arm B (docetaxel): Day 1 of cycle 2 and subsequently on Day 1 of every cycle (every 3 weeks) on study treatment, and at the first 2 follow-up visits after discontinuation of study treatment

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a subject or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an

abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

6.1 Serious Adverse Events

A ***serious AE (SAE)*** is any untoward medical occurrence that at <u>any dose</u>:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires insubject hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

Suspected transmission of an infectious agent (eg, any organism, virus or infectious particle, pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, cancer, and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs. (See Section 6.1.1 for reporting pregnancies).

NOTE:

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was planned prior to entry into the study. Appropriate documentation is required in these cases
- admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

6.1.1 Serious Adverse Event Collection and Reporting

Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing (within 30 days of last visit for enrollment/ screening failures). If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its status of seriousness.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). When using paper forms, the reports are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: See Contact Information list

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted

immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

SAE Telephone Contact (required for SAE and pregnancy reporting): See Contact Information list.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

A ***nonserious adverse event*** is an AE not classified as serious.

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF (paper or electronic).

All nonserious adverse events (not only those deemed treatment-related) are to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

Completion of supplemental CRFs may be requested for AEs and/or laboratory abnormalities that are reported/identified during the course of the study.

6.3 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured on the nonserious AE CRF page or SAE Report Form (paper or electronic) as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical, rather than the laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to the sponsor. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

6.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE (see Section 6.1.1 for reporting details).

6.6 Potential Drug Induced Liver Injury (DILI)

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs (see Section 6.1.1. for reporting details).

Potential drug induced liver injury is defined as

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),

AND

3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

For recommendations regarding suspected pulmonary toxicity, diarrhea and colitis, suspected hepatotoxicity (including asymptomatic LFT elevations), or suspected endocrinopathy, please see the Evaluation and Management Guidelines found in the Investigator Brochure.[20]

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209017, and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for BMS-936558 (nivolumab). The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. Efficacy will also be reviewed by the DMC - as part of the benefit-to-risk assessment at safety interim reviews, and for the formal interim analysis of overall survival (OS).

The DMC will be advisory to the clinical study leadership team. The clinical study leadership team will have responsibility for overall conduct of the study including managing the communication of study data. The group will be responsible for promptly reviewing the DMC recommendations, for providing guidance regarding the continuation or termination of the study, and for determining whether amendments to the protocol or changes in study conduct are required.

After meeting, the DMC will notify the clinical study leadership group that it has met and will provide recommendations about the study by telephone or email. Detailed procedures to deliver and address the DMC recommendations are described in the BMS Standard Operating Procedure, which specifies the establishment and operation of clinical trial DMCs. Any recommendation by the DMC regarding study modification will be submitted to the clinical study leadership team within pre-specified business days of the DMC meeting.

The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study. Details of DMC responsibilities and procedures will be specified in the DMC charter.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Results from ipilimumab phase 3 studies in metastatic melanoma patients [63,64] have demonstrated long term survival benefits in patients treated with ipilimumab observed as a long lasting plateau towards the tail of the survival curve. Results also suggested a delayed effect

observed as late separation of survival curves between experimental and control arms of the studies. Both long-term survival and delayed onset of benefit may be particular to immuno-oncology drugs based on their mechanisms of action. .

The final analysis of OS will be conducted when at least 231 deaths have been observed among 272 randomized subjects. Accrual rates are based on observed accrual, with full randomization of 272 subjects completed in 14 months. Power calculations were performed using Power Analysis & Sample Size Software® (PASS [65]). Given the observed accrual and the survival assumptions it is expected that the duration of the study from start of randomization to final analysis will be approximately 38 months (14 months for accrual and 24 months minimum survival follow-up). One formal interim analysis for superiority of OS is planned after 196 deaths (85% of deaths required for final analysis) have been observed. The cumulative power up to interim and final OS analysis will be 55% and 90% respectively.

Additional details on power calculations are documented in statistical analysis plan.

The secondary endpoints of investigator-assessed ORR and PFS will be tested hierarchically (see Section 8.4.2).

Table 8.1-1 summarizes the key parameters of the overall survival analysis.

Table 8.1-1: Key Parameters of the Overall Survival Analysis

	Analysis	Timing	Critical Value for significance	Probability for declaring superioritiy Under H1/H0
α= 0.05; Power=90%	Interim analysis for superiority	196 deaths	p < 0.030	55% / 3%
Docetaxel arm: **Exponential distribution with median OS= 7 months** **Nivolumab arm:** **Piecewise mixture distribution with median OS= 8.9 months**	Final analysis for superiority	231 deaths	p < 0.041	35%/ 2%
Total probability to declare superiority Under H1/H0				90% / 5%

8.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS. Analyses of the patients enrolled into the study but not randomized and the reason for not being randomized will be performed on the data set of all enrolled subjects
- All randomized subjects: All subjects who were randomized to any treatment arm in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and PD-L1expression.
- All treated subjects: All subjects who received at least one dose of BMS-936558 (nivolumab) or docetaxel. This is the primary dataset for dosing and safety
- Response Evaluable Subjects: randomized subjects whose change in the sum of diameters of target lesions was assessed (ie. target lesion measurements were made at baseline and at least one on-study tumor assessment.)
- Immunogenicity evaluable subjects: All BMS-936558 (nivolumab) treated subjects with baseline and at least 1 post-baseline immunogenicity assessment
- All PD-L1 Tested subjects: All subjects, randomized or not, who had a tumor biopsy specimen available for PD-L1 expression testing. This includes both randomized and screen failure subjects.

8.3 Endpoint Definitions

8.3.1 Primary Endpoint

The primary objective in the study will be measured by the primary endpoint of OS.

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at last known date alive. OS will be followed continuously while subjects are on the study drugs and every 3 months via in-person or phone contact after subjects discontinue the study drugs.

8.3.2 Secondary Endpoints

8.3.2.1 ORR

The first secondary objective (to compare ORR) will be measured by the key secondary endpoint of investigator-assessed ORR in each randomized arm, duration of objective response (DOR) and time to objective response (TTR) in each randomized arm. ORR (as determined by the investigator) is defined as the number of subjects whose best confirmed objective response is either a CR or PR divided by the number of randomized subjects. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For

subjects who continue BMS-936558 (nivolumab) beyond progression, the BOR should be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

DOR is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy. TTR is defined as the time from randomization to the date of the first confirmed CR or PR. DOR and TTR will be evaluated for responders (confirmed CR or PR) only.

8.3.2.2 PFS

PFS is defined as the time from randomization to the date of the first documented tumor progression as determined by the investigator (per RECIST 1.1), or death due to any cause. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on initiation of the subsequent anti-cancer therapy.

8.3.2.3 PD-L1 Protein Expression

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay.

Baseline PD-L1 expression: If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment) with a quantifiable result. If all specimens for a given subject are either indeterminate or not evaluable, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered not evaluable.

8.3.2.4 Disease-Related Symptom Improvement Rate by Week 12

Disease-related Symptom Improvement Rate by Week 12 is defined as the proportion of randomized subjects who had 10 points or more decrease from baseline in average symptom burden index score at anytime between randomization and week 12. The patient portion of the LCSS scale consists of a six symptom-specific questions that adress cough, dyspnea, fatigue, pain, hemoptysis, and anorexia, plus three summary items on symptom distress, interference with activity level, and global health-related quality of life (HRQL)[66,67]. The degrees of impairment is

recorded on a 100mm visual analogue scale, with scores reported from 0 to 100 and 0 representing the best score. The average symptom burden index score at each assessment will be computed as the mean of the six symptoms specific questions of the LCSS. The average symptom burden index score is ranging from 0 to 100, with zero being the best possible score and 100, the worst possible score.

The LCSS questionnaire is completed on Day 1 of the scheduled cycle for the first 6 months on study treatment, then every 6 weeks thereafter for the remainder of the study, and at the first two follow-up visits. See Table 5.1-2, and Table 5.1-3 (and Table 5.1-4 for Follow-up visits) for frequency of assessments on study for each treatment arm.

8.3.3 Exploratory Endpoints

Safety and tolerability objective will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Adverse event assessments and laboratory tests are performed at baseline, and continuously throughout the study at the beginning of each subsequent cycle.

The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of BMS-936558 (nivolumab) and to explore exposure-safety and exposure-efficacy relationships.

Other exploratory endpoints for pharmacogenomics, immunogenicity and outcomes research are discussed in detail in Sections 8.4.5, 8.4.6 and 8.4.7.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline laboratory results will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

All hypothesis testing will be two-sided based on a significance level of 0.05 except for OS. A group sequential testing procedure will be applied to OS to control the overall type I error for interim and final analyses (overall alpha=0.05). If superiority in OS is demonstrated, a hierarchical hypothesis testing approach for the key secondary endpoints will be used to preserve a study-wise type I error rate at 0.05. The key secondary endpoints will be tested in the following hierarchical order:

1.) ORR

2.) PFS

The formal statistical testing for ORR will take place only if OS is statistically significant and the statistical testing for PFS will take place only if both OS and ORR are statistically significant.

8.4.2.1 Methods of Primary Endpoint

The distribution of OS will be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified by the same factors above. The hazard ratio (HR) and the corresponding 100x (1-adjusted alpha) % confidence interval (CI) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The OS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be computed by Brookmeyer and Crowley method (using log-log transformation). Survival rates at 6, 12, 18, 24, 36, 48 months and 5 years will also be estimated using KM estimates on the OS curve for each randomized arm. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation). The status of subjects who are censored in the OS Kaplan-Meier analysis will be tabulated for each treatment group. Assumption of proportional hazards in the Cox regression model will be examined by adding a time-dependent defined by treatment by time interaction in the model. Sensitivity analyses of OS will also be performed. Consistency of treatment effect on OS in pre-defined subsets will be assessed using forest plots. To assess the treatment effect on OS after adjusting for pre-defined potential prognostic factors, a multivariate stratified Cox model will be fitted.

8.4.2.2 Methods for Secondary Endpoint

ORR in two randomized arms will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by prior use of paclitaxel vs. no paclitaxel use, and region. An associated odds ratio and 95% CI will be calculated. ORR and their corresponding 95% exact CI will be calculated by Clopper-Pearson method for each randomized arm.

Summary statistics of time to objective response (TTR) will be provided for each treatment group for subjects who achieve PR or CR. Duration of response (DOR) in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

The distribution of PFS will 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 region (US vs Europe vs Rest of World).

HR and corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each treatment group will be estimated using the KM product-limit method. Two sided, 95% confidence intervals for median PFS will be computed using a log-log transformed CI for the survivor function S(t). PFS rates at 6, 12, 18, 24, 36, 48 months and 5 year will be estimated using KM estimates on the PFS curve for each randomized arm provided minimum follow-up is longer than timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood formula (using log-log transformation).

Disease-related symptom improvement rate (as measured by LCSS) by Week 12 and its corresponding 95% exact CI will be calculated for each treatment group, using the Clopper-Pearson method. Baseline and change from baseline of the average symptom burden scale index

score at each LCSS assessment point will be summarized using descriptive statistics (N, mean, median, SD) by treatment group, as randomized.

Analyses of PD-L1 expression will be descriptive. Distribution of PD-L1 expression will be examined based on overall population. Potential associations between PD-L1 expression and efficacy measures (ORR, OS, PFS) will be assessed. ORRs will be computed by treatment group along with exact 95% CIs using the Clopper-Pearson method for each PD-L1 Expression subgroup. Associated odds ratios and 95% CIs will be calculated. OS/PFS curves for each randomized arm will be estimated using the Kaplan-Meier (KM) product-limit method for each PD-L1 Expression subgroup. Two-sided, 95% confidence intervals for median OS/PFS will be computed by Brookmeyer and Crowley method (using log-log transformation). If there is an indication of a meaningful association, future work will evaluate PD-L1 expression as a predictive biomarker, including selection of an optimal PD-L1 expression cut-off to classify subjects as PD-L1 positive or PD-L1 negative. Cut-off selection and validation will be conducted across studies.

8.4.3 Safety Analyses

The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 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 will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinisic covariates on the PK of BMS-936558 (nivolumab) and to determine measures of individual exposure (such as steady-state peak, trough, and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety end points. Results of population PK and exposure response analyses will be reported separately.

8.4.5 Biomarker Analyses

Pharmacodynamic Analyses

To assess pharmacodynamic effects in serum obtained from subjects on each treatment arm, summary statistics for biomarkers of immunoregulatory activity (eg IFNγ-inducible proteins, miRNAs, antibodies to tumor antigens) and their corresponding changes (or percent changes) from baseline will be tabulated by planned study visit. In addition, the time course of biomarker outcomes will be investigated graphically. If there is indication of a meaningful pattern across time, further analysis may be completed to characterize the relationship. Possible associations

between changes in biomarker measures of interest and exposure to study drug will be explored graphically.

Pharmacogenomic and Exploratory Analyses

Potential relationships between biomarker data and efficacy or safety endpoints will be investigated as part of an analysis plan aimed at identifying baseline biomarkers that may be used to prospectively identify subjects likely (or not likely) to respond to BMS-936558 (nivolumab) and to identify subjects who may be predisposed to having adverse reactions to treatment. These exploratory predictive biomarker analyses will be completed with biomarkers measured in blood and in tumor samples and will focus primarily- as outlined in the exploratory objectives- on SNPs in select genes associated with immunity or on the expression of PD-1, PD-L1, and PD-L2 proteins in tumor specimens. Similar analyses will be completed with data regarding serum-soluble factors, serum miRNA content, and putative additional analyses to be completed using FFPET.

Associations between biomarkers and efficacy measures will be analyzed on all randomized subjects with available biomarker data. Efficacy measures will include response, PFS, and OS. Demographic and case-history factors will be examined to determine whether stratification or adjustments should be made within the subsequent statistical analyses, and if necessary, the appropriate stratification or adjustment will be made.

Biomarkers will be summarized graphically as they relate to efficacy and safety endpoints, as applicable. Summary statistics will be tabulated. SNP allele frequencies will be summarized. The relationships between binary measures (eg. response) and candidate biomarkers will be investigated using logistic regression. Associations will be summarized in terms of point and interval estimates of hazard ratios, odds ratios, or other statistics, as appropriate for the analyses completed. Models to predict clinical activity based on combinations of biomarkers may also be investigated.

Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches may be completed. All analyses described in this section are based on the availability of the data.

8.4.6 Outcomes Research Analyses

LCSS questionnaire complete rate, defined as the proportion of questionnaires actually received out of the expected number (ie, the number of subjects still on treatment in follow-up), will be calculated and summarized at each assessment point..

The EQ-5D will be used to assess the subject's overall health status. EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state [68,69,70]

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics by treatment group, as randomized.

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized. Percentages will be based on number subjects assessed at assessment time point.

Summary statistics will be calculated for the population preference-based health state utility score (EQ-5D Index).

8.4.7 Other Analysis

Methodology for exploratory analyses including immunogenicity, other HRQoL assessments (PRO), and healthcare resource utilization is described in the statistical analysis plan.

8.5 Interim Analyses

One interim analysis of OS is planned after 196 deaths (85% of deaths required for final analysis) have been observed. This formal comparison of OS will allow for early stopping for superiority.

The OS comparison will be tested using the interim monitoring feature of EAST v5.4 software based on a generalization of the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to reject H0, controlling for a two-sided overall α of 5%. If exactly 196 deaths are in the locked database at the interim analysis, H0 would be rejected if the p-value from the log-rank test is $p < 0.030$. If the number of deaths is not exactly 196 at the time of the interim analysis, the nominal critical point and value of both the interim and final analyses will be calculated based upon the observed information fraction. An independent statistician external to BMS will perform the analysis and DMC will review.

If the study continues beyond the interim analysis, the nominal significance level for the final look after 231 deaths would be 0.041. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol, final boundary will not be recalculated using updated information fraction at interim.

In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Bristol-Myers Squibb
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

In addition, the study may be evaluated by BMS internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities, and promptly forward copies of inspection reports to BMS.

9.1.3 Investigational Site Training

Bristol-Myers Squibb will provide quality investigational staff training prior to study initiation. Training topics will include but are not limited to: GCP, AE reporting, study details and procedure, electronic CRFs, study documentation, informed consent, and enrollment of WOCBP.

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by the sponsor, whichever is longer. The investigator must contact BMS prior to destroying any records associated with the study.

BMS will notify the investigator when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) maintained at each study site where study drug and the following noninvestigation product(s) dexamethasone is inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number
- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

BMS will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data reported on the CRF that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by the sponsor.

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by a qualified physician who is an investigator or subinvestigator, and who is delegated this task on the Delegation of Authority Form. For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by the sponsor. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee
- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

The data collected during this study are confidential and proprietary to the sponsor. Any publications or abstracts arising from this study require approval by the sponsor prior to publication or presentation and must adhere to the sponsor's publication requirements as set forth in the approved clinical trial agreement (CTA). All draft publications, including abstracts or detailed summaries of any proposed presentations, must be submitted to the sponsor at the earliest practicable time for review, but at any event not less than 30 days before submission or presentation unless otherwise set forth in the CTA. Sponsor shall have the right to delete any confidential or proprietary information contained in any proposed presentation or abstract and may delay publication for up to 60 days for purposes of filing a patent application.

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or the sponsor as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)

11 LIST OF ABBREVIATIONS

ADA	Anti-drug antibody
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic lymphoma kinase (CD246)
ALT	Alanine Aminotransferase
APC	Antigen-presenting cells
AST	Aspartate Aminotransferase
Bcl- x_L	B-cell lymphoma-extra large
BID	Twice per day
B7-DC	Human B7 –dendritic cell
B7-H1	Human B7 homolog 1
BMS	Bristol-Myers Squibb
BSC	Best supportive care
BTLA	B-and T-cell attenuator
CD28	Cluster of differentiation 28
CD273	Cluster of differentiation 273
CD274	Cluster of differentiation 274
C57BL/6	C57 black 6 breed mouse
CI	Confidence interval
CMV	Cytomegalovirus
CNS	Central nervous system
COX2	Cyclooxygenase-2
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTA	Clinical trial agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T-Lymphocyte
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
CYP	Cytochrome P450
D	Day
DCF	Data clarification form
DILI	Drug induced liver injury
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DOOR	Duration of objective response
ECL	Electrochemilumeminescent
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture

EGFR	Epidermal growth factor receptor
EI	Equivalence interval
ELISA	Enzyme-Linked Immunosorbent Assay Test
EOI	End-of-infusion
ESOI	Events of special interest
EU	European Union
FFPET	Formalin-fixed, paraffin-embedded tumor tissue
FLIP	caspase-8 (FLICE)-like inhibitory protein
FSH	Follicle stimulating hormone
FU	Follow up
GCP	Good clinical practices
GMP	Good manufacturing practices
HCG	Human Chorionic Gonadotropin
HIPAA	Health Information Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HLA	Human leukocyte antigen
HR	Hazard ratio
HTA	Health authority
ICF	Informed consent form
ICH	International Conference on Harmonisation
ICOS	Inducible T-cell co-stimulator (CD278)
IDO	Inducible co-stimulator
IFN	Interferon
IFNGR1	Interferon Gamma-receptor-1
IFN-γ	Interferon Gamma
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry
IL	Interleukin
ITIM	Immunoreceptor tyrosine inhibitory motif
ITSM	Immunoreceptor tyrosine-based switch motif
IRB/IEC	Institutional review board/independent ethics committee
IV	Intravenous
IVRS	Interactive voice response system
KM	Kaplan-Meier curve
LMP	Low-molecular-mass protein
mAb	Monoclonal antibody
mCRPC	Metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MEL	Metastatic melanoma
mg	Milligram
mL	Milliliter

MLR	Mixed Lymphocyte Reaction
MRI	Magnetic resonance imaging
MTD	Maximum-tolerated dose
M^2	Square meter
NCI	National Cancer Institute
NK	Natural killer
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small-cell lung cancer
NOS	Not otherwise specified
NOS2	Nitric oxide synthase 2
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PGE2	Prostaglandin E2
PK	Pharmacokinetics
PO	By mouth
P19	Serine-protease inhibitor
PR	Partial response
PRO	Subject reported outcomes
PSA	Prostate-specific antigen
PVG	Pharmacovigilance
q	Every
PRO	Patient reported outcomes
RAG	Recombination activating gene
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radiation therapy
SAE	Serious adverse event
SD	Stable disease
SLD	Sum of longest diameters
SNP	Single nucleotide polymorphism
SOC	System/Organ/Class
SOP	Standard operating procedures
Src	Sarcoma
STAT	Signal Transducers and Activators of Transcription

TAP1	Transporter associate with antigen processing 1
TCR	T-cell receptor
TEAE	Treatment-emergent adverse event
TGF	Transforming growth factor
TIL	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TNF	Tumor necrosis factor
TRAIL	Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Treatment
Tregs	Regulatory T cells
TTOR	Time to objective response
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of child bearing potential

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APPENDIX 1 RECIST 1.1 CRITERIA

This Appendix has been excerpted from the full RECIST 1.1 criteria. For information pertaining to RECIST 1.1 criteria not contained in the study protocol or in this Appendix, please refer to the full publication.[1]

1 ASSESSMENT OF OVERALL TUMOR BURDEN AND MEASURABLE DISEASE

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion.

1.1 Measurability of tumor

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of the measurement to be recorded) with a minimum size of:

- 10 mm by CT scan - (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All measurements should be recorded in metric notation, using calipers if clinically assessed.

Special considerations regarding lesion measurability

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions are all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as non-measurable lesions. Lesions considered non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.2 Method of assessment

The **same method of assessment and the same technique should be used** to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be performed rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical examination.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Chest x-ray: Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint, since CT is more sensitive than x-ray, particularly in identifying new lesions. However, lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

2 BASELINE DOCUMENTATION OF 'TARGET' AND 'NON-TARGET' LESIONS

Target lesions: When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3 TUMOR RESPONSE EVALUATION AND RESPONSE CRITERIA

3.1 Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Note: the appearance of one or more new lesions is also considered progression.

Stable Disease (SD): Neither sufficient shrinkage from the baseline study to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

- **Lymph nodes:** Lymph nodes identified as target lesions should always have the actual short axis measurement recorded and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.
- **Target lesions that become 'too small to measure':** All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

However, when such a lesion becomes difficult to assign an exact measure to then:

(i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.

(ii) if the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.2 Evaluation of non-target lesions

While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

- The concept of progression of non-target disease requires additional explanation as follows:
- *When the patient also has measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.
- *When the patient has only non-measurable disease*: To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point.

3.3 New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain

ordered which reveals metastases. The patient's brain metastases are considered to be constitute PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents new disease. If repeat scans confirm that there is a new lesion, then progression should be declared using the date of the initial scan.

3.4 Tumor markers

Tumor markers alone cannot be used to assess objective tumor responses. If markers are initially above the upper normal limit, however, they must normalize in order for a patient to be considered as having attained a complete response.

4 EVALUATION OF BEST OVERALL RESPONSE

4.1 Time point response

A response assessment should occur at each time point specified in the protocol.

For patients who have measurable disease at baseline Appendix Table 1 provides a summary of the overall response status calculation at each time point.

Table 1: Appendix Table 1 - Summary of the Overall Response Status Calculation [Time point response - patients with target (+/-) non-target disease]

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

4.2 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

4.3 Best overall response: all timepoints

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol. In this circumstance, the best overall response can be interpreted as in Appendix Table 2.

Table 2: Appendix Table 2 - Best overall response when confirmation of CR and PR required

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4 Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression

even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Appendix Table 1 and Table 2.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

5 ADDITIONAL CONSIDERATIONS

5.1 Duration of response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

5.2 Lesions that disappear and reappear

If a lesion disappears and reappears at a subsequent time point it should continue to be measured. However, the patient's response at the point in time when the lesion reappears will depend upon the status of his/her other lesions. For example, if the patient's tumour had reached a CR status and the lesion reappeared, then the patient would be considered PD at the time of reappearance. In contrast, if the tumour status was a PR or SD and one lesion which had disappeared then reappears, its maximal diameter should be added to the sum of the remaining lesions for a calculated response: in other words, the reappearance of an apparently 'disappeared' single lesion amongst many which remain is not in itself enough to qualify for PD: that requires the sum of all lesions to meet the PD criteria. The rationale for such a categorization is based upon the realization that most lesions do not actually 'disappear' but are not visualized because they are beyond the resolving power of the imaging modality employed.

5.3 Use of FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. Confirmatory CT is recommended.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up:

- If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.
- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

Reference:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. (2009); 45:228-247.

APPENDIX 2 GUIDANCE ON CONTRACEPTION[1, 2, 3, 4, 5, 6, 7, 8]

ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 3 OPTIONS)[a]

OPTION 1: Any TWO of the following methods

- Hormonal methods of contraception[b, c, d]
- IUD[c, d, e]
- Vasectomy[d, f]
- Tubal Ligation[d]
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm[g]

OPTION 3: Male condom (with spermicide) and cervical cap[g]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year

[b] Excludes progestin-only pills

[c] Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The PK scientist and MST chair must agree that the use of hormone-based contraception is safe and efficacious for WOCBP. The use of hormone-based contraceptives is not otherwise restricted

[d] A highly effective method of birth control with a failure rate less than 1% per year

[e] IUDS used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard

[f] Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia

[g] These 2 barrier methods together are acceptable for a teratogenic drug

UNACCEPTABLE METHODS OF CONTRACEPTION

Abstinence (including periodic abstinence)

No method

Withdrawal

Rhythm

Vaginal Sponge

Any barrier method without spermicide

Spermicide

Progestin only pills

Concomitant use of female and male condom

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of > 1%.

Women of childbearing potential (WOCBP) receiving BMS-936558 (nivolumab) will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving BMS-936558 (nivolumab) and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for BMS-936558 (nivolumab) (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of BMS-936558 (nivolumab).

For women of childbearing potential (WOCBP) randomized to receive docetaxel, they will be instructed to adhere to contraception for a period of 33 days after the last dose of investigational product.

Men randomized to receive docetaxel must follow instructions for birth control as per the SmPC (6 months after discontinuation of treatment), or package insert.

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[7] MHRA: Clarification of contraceptive wording in clinical trials in the UK. Version 2-amended 21 May 2010.

[8] International Conference of Harmonization (ICH) Guidance for Industry M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, M3 (R2) January 2010.

STATISTICAL ANALYSIS PLAN
FOR CLINICAL STUDY REPORT

AN OPEN-LABEL RANDOMIZED PHASE III TRIAL OF NIVOLUMAB (BMS-936558) VERSUS DOCETAXEL IN PREVIOUSLY TREATED ADVANCED OR METASTATIC SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

PROTOCOL(S) CA209-017

VERSION # 2.0

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 BACKGROUND AND RATIONALE

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, accounting for approximately 18% of all cancer deaths Unlike patients with non-squamous histology NSCLC, patients with squamous cell NSCLC have generally not benefitted from (and in fact may be negatively impacted by) several new agents, including pemetrexed and bevacizumab. Therapeutic options for squamous cell NSCLC are particularly limited after failure of treatment-naïve chemotherapy. Therefore, while representing a minority of NSCLC cases, squamous cell NSCLC remains a disease with high burden and unmet medical need.

Nivolumab is a fully human, IgG4 (kappa) isotype, PD-1 receptor blocker mAb that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response.

CA209-017 is a randomized, open-label, multinational Phase 3 trial of nivolumab monotherapy versus docetaxel in subjects with squamous cell NSCLC whose disease has progressed during or after one prior platinum doublet-based chemotherapy regimen. The central question of the study will be to determine if nivolumab improves overall survival (OS) over the comparator in this patient population. Additional objectives include further characterization of the efficacy, adverse event profile, pharmacokinetics, patient-reported outcomes, and potential predictive biomarkers of nivolumab in subjects with squamous cell NSCLC.

This statistical analysis plan (SAP) details all analyses that are planned in the Clinical Study Report (CSR) for CA209017 study except for safety which will be documented separately in the Core Safety SAP[1].

Research Hypothesis:

Nivolumab increases OS as compared with docetaxel, in squamous cell NSCLC subjects treated with prior platinum doublet-based chemotherapy.

Schedule of Analyses:

One formal interim analysis for superiority of OS is planned when at least 196 deaths have been observed, which would occur approximately 26 months after start of randomization (14 months accrual, minimum 12 month follow-up for survival). At OS interim analysis, the trial may be stopped or continued based on recommendation from the Data Monitoring Committee (DMC). Details are specified in the DMC charter[2]. If the trial is continued at the time of the OS interim analysis, the final analysis for superiority of OS will then take place when at least 231 deaths have been observed (approximately 38 months after start of randomization). Additional survival follow-up may continue for up to 5 years from the time of this analysis. The study will end once survival follow-up has concluded.

All secondary endpoints will be analyzed at the time of the final analysis of OS. In the event that the interim analysis for superiority of OS is positive, final CSR analyses may be performed prior to achieving 231 deaths; additional details can be found in Section 5.

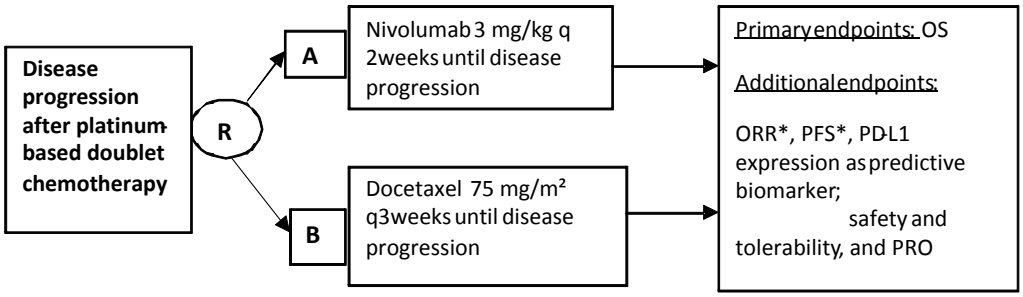
2 STUDY DESCRIPTION

2.1 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. Subjects will undergo screening evaluations to determine eligibility within 28 days prior to randomization. Subjects will be randomized to the two treatment groups in a 1:1 ratio (see Figure 2.1-1 below). Randomization will be stratified according to the following factors: prior treatment with paclitaxel-based doublet vs. other doublet, and region (US vs. Europe vs. Rest of World).

This study will consist of 3 phases: screening, treatment, and follow-up (see descriptions in protocol).

Figure 2.1-1: Study Design



*tumor response and progression as determined by the investigator using RECIST 1.1 criteria

2.2 Treatment Assignment

Subjects are enrolled using the Interactive Voice Response System (IVRS) to obtain a subject ID. Subjects who have signed informed consent and met all eligibility criteria will be ready to be randomized through the IVRS, upon confirmation of receipt of required tissue sample by the central lab. The following information is required for subject randomization:

- Subject number.
- Date of birth.
- Gender at birth.
- Diagnosis.
- Date of informed consent.
- Prior paclitaxel vs. other prior treatment.
- Region (US/ Canada vs. Europe vs. Rest of World).

Subjects will be randomly assigned through IVRS in 1:1 ratio to either arm A (nivolumab) or arm B (docetaxel) stratified by the following factors: prior paclitaxel vs. other prior treatment, and region. The randomization will be carried out via permuted blocks within each stratum.

2.3 Blinding and Unblinding

Not applicable. This is an open-label study.

2.4 Protocol Amendments

This SAP incorporates following protocol amendments.

Table 2.4-2: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Revised Protocol 03	25-Apr-2014	• Modification to the overall survival (OS) analysis, relative to the number of required events and timing of interim and final OS analyses. Changes made to address observations of long-term survival and delayed onset of benefit in studies with immuno-oncology drugs. • Objective response rate (ORR) moved from a co-primary endpoint to a secondary endpoint (OS remains as the sole primary endpoint). Modification based on mature ORR results from an expanded cohort of NSCLC subjects treated in the Phase 1b study MDX1106-03. ORR per investigator (IRC removed) is the first secondary endpoint to be tested in the statistical hierarchy if OS is positive, at either the interim or final OS analysis
Revised Protocol 02 (Incorporates Amendment 07)	28-May-2013	• In response to a request of the US FDA, the trial was modified to require confirmation of objective response per RECIST 1.1 criteria • Clarification of the target population • Extension of OS analyses to 5 years beyond the primary OS analysis • Collection of PRO information during the survival phase • Modification of the secondary objective related to analysis of efficacy data by PD-L1 expression status • Modification of the secondary objective related to analysis of PRO • Modification of the tumor assessment schedule for non-progressing subjects who initiate a subsequent anticancer therapy • Inclusion of additional safety information on BMS-936558 (nivolumab) for opportunistic infections related to immunosuppression • The inclusion of "nivolumab" throughout the protocol, as the approved generic name for BMS-936558
Revised Protocol 01 (Incorporates Amendment 06)	08-Mar-2013	• Section 1.4.3.2 Safety Summary was updated to include language on preliminary new non-clinical safety findings of adverse pregnancy outcomes • Section 3.3.1 Criteria 3a and 3d were updated to add clarifying language related to duration of contraception • Appendix 2 was updated to revise the acceptable methods table, and add new language at the end of the appendix.

Table 2.4-2: Protocol Amendments

Amendments	Date of Issue	Summary of Major Changes
Original Protocol	12-Jun-2012	• Not Applicable

2.5 Data Monitoring Committee

A DMC will be established to provide oversight of safety and efficacy considerations and to provide advice to the Sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the trial. Details of DMC responsibilities and procedures will be specified in the DMC charter2.

3 OBJECTIVES

3.1 Primary

To compare the OS of nivolumab versus docetaxel in subjects with squamous cell NSCLC after failure of prior platinum-based chemotherapy.

3.2 Secondary

Secondary objectives include the following:

- To compare the ORR of nivolumab versus docetaxel
- To compare the progression-free survival (PFS) of nivolumab versus docetaxel.
- To evaluate whether PD-L1 expression is a predictive biomarker for OS ,ORR or PFS.
- To evaluate the proportion of subjects exhibiting disease-related symptom improvement by Week 12, as measured by LCSS, in nivolumab and docetaxel groups.

3.3 Exploratory Objectives

- To assess the overall safety and tolerability of nivolumab versus docetaxel.
- To explore potential predictive biomarkers of nivolumab efficacy (such as ORR, PFS or OS) in peripheral blood and tumor specimens, including antibodies to tumor antigens and proteins involved in regulating immune responses (e.g. PD-1, PD-L1, PD-L2).
- To assess the effects natural variation single nucleotide polymorphism (SNPs) in select genes (e.g. PD-1, PD-L1, PD-L2, CTLA-4) has on clinical endpoints and/or on the occurrence of adverse events.
- To characterize immunogenicity of nivolumab.
- To characterize pharmacokinetics of nivolumab and explore exposure-response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints.
- To assess the subject's overall health status using the EQ-5D Index and visual analog scale.

4 ENDPOINTS

4.1 Primary Endpoints

OS is defined as the time from randomization to the date of death. A subject who has not died will be censored at the last known date alive.

4.2 Secondary Endpoints

4.2.1 Investigator-Assessed Objective Response Rate

ORR is defined as the number of subjects whose best confirmed objective response (BOR) is either a confirmed CR or confirmed PR, as determined by the investigator, divided by the number of randomized subjects. BOR is defined as the best response designation, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions), whichever occurs first. For subjects without documented progression or subsequent anti-cancer therapy, all available response designations will contribute to the BOR determination. For subjects who continue nivolumab treatment beyond progression, the BOR will be determined based on response designations recorded up to the time of the initial RECIST 1.1-defined progression.

Duration of objective response (DOR) is defined as the time between the date of first confirmed response to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Subjects who neither progress nor die will be censored on the date of their last evaluable tumor assessment. Subjects who started any subsequent anti-cancer therapy (excluding on-treatment palliative radiotherapy of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy. DOR will be evaluated for responders (i.e. subjects with confirmed CR or PR) only.

Duration of Stable Disease is defined as the time from the randomization date to the date of the first documented tumor progression (per RECIST 1.1), or death due to any cause, whichever occurs first. Censoring rules will be the same as for DOR analysis. Duration of stable disease will be evaluated for subjects with stable disease as BOR.

Time to Objective Response (TTR) is defined as the time from randomization to the date of the first confirmed response. TTR will be evaluated for responders only.

4.2.2 Progression -Free Survival

Progression -Free Survival (PFS) is defined as the time from randomization to the date of the first documented tumor progression as determined by the investigator using RECIST 1.1 criteria, or death due to any cause. Clinical deterioration in the absence of unequivocal evidence of progression (per RECIST 1.1) is not considered progression for purposes of determining PFS. Subjects who die without a reported prior progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and

did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy (including on-treatment palliative RT of non-target bone lesions or CNS lesions) without a prior reported progression will be censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy.

Table 4.2.2-2: Censoring scheme used in primary analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization date	Censored
No on-study tumor assessments and no death	Randomization date	Censored
New anticancer treatment started without a prior reported progression per RECIST 1.1 or death	Date of last evaluable tumor assessment prior to or on the date of initiation of the subsequent anti-cancer therapy	Censored
Progression per RECIST 1.1 documented at a scheduled or unscheduled visit and no new anticancer treatment started before	Date of the first documented tumor progression	Progressed
Subject progression free and no new anticancer treatment started	Date of last evaluable tumor assessment	Censored
Death without prior progression per RECIST 1.1 and no new anticancer treatment started	Date of death	Progressed

4.2.3 PD-L1 Expression

PD-L1 expression missing: Subjects without an available tumor biopsy specimen for PD-L1 evaluation will be considered as PD-L1 expression missing.

For subjects with an available tumor biopsy specimen(s), the following will be considered:

PD-L1 expression is defined as the percent of tumor cell membrane staining in a minimum of 100 evaluable tumor cells per validated Dako PD-L1 IHC assay. The following different categories of PD-L1 expression are considered in this study:

Quantifiable: Subjects with an available tumor biopsy specimen and number of viable tumor cells per validated Dako PD-L1 IHC assay is ≥ 100 and percentage of tumor PD-L1+ is ≥ 0%.

Indeterminate: Subjects with an available tumor biopsy specimen but tumor cell membrane staining hampered for reasons attributed to the biology of the tumor biopsy specimen and not because of improper sample preparation or handling

Not evaluable: Subjects with an available tumor biopsy specimen but tumor biopsy specimen was not optimally collected or prepared (e.g. PD-L1 expression is neither quantifiable nor indeterminate). Not evaluable will be determined from H&E process before the tumor biopsy specimen is sent for PD-L1 evaluation or from the H&E process during PD-L1 evaluation.

Baseline PD-L1 expression: If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment or prior to randomization date for subjects randomized but never treated) with

a quantifiable result. If all specimens for a given subject are either indeterminate or not evaluable, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered not evaluable.

PD-L1 status at Baseline:

- **PD-L1 Positive**: subjects with baseline PD-L1 expression ≥ x% cutoff value
- **PD-L1 Negative**: Subjects with baseline PD-L1 expression < x% cutoff value and ≥ 0%
- **PD-L1 Not Quantifiable :** Subjects with no quantifiable PD-L1 expression at baseline

The following cut-off values will be explored: 1%, 5% and 10%.

4.2.4 Disease-Related Symptom Improvement Rate by Week 12

Disease-Related Symptom Improvement Rate by Week 12 is defined as the proportion of randomized subjects who had 10 points or more decrease from baseline in average symptom burden index score at anytime between randomization and week 12.

The patient portion of the LCSS scale consists of six symptom-specific questions that address cough, dyspnea, fatigue, pain, hemoptysis, and anorexia, plus three summary items on symptom distress, interference with activity level, and global HRQL. The degree of impairment is recorded on a 100-mm visual analogue scale, with scores reported from 0 to 100 and 0 representing the best score. The average symptom burden index score at each assessment will be computed as the mean of the six symptoms-specific questions of the LCSS. The average symptom burden index score is ranging from 0 to 100, with zero being the best possible score and 100, the worst possible score.

4.3 Exploratory Endpoints

4.3.1 Safety and Tolerability

Safety will be analyzed through the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade) in each treatment group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP.

4.3.2 Immunogenicity

Please refer to core safety SAP

4.3.3 Outcomes Research

Patients' overall health status will be assessed using the The EuroQol Group's self-reported health status measure (EQ-5D)[3]. EQ-5D essentially has 2 components - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)[4].

5 SAMPLE SIZE AND POWER

The sample size is calculated in order to compare the overall survival (OS) between subjects randomized to receive nivolumab and subjects randomized to receive docetaxel.

Recent results from ipilimumab phase 3 studies[5,6], in metastatic melanoma patients have demonstrated long term survival benefits in patients treated with ipilimumab observed as long lasting plateau towards the tail of survival curve. Results also suggested a delayed effect observed as late separation of survival curves between experimental and control arms of the studies. Both long-term survival and delayed onset of benefit may be particular to immuno-oncology drugs based on their mechanisms of action. Consequently, simulations have been performed using Power Analysis & Sample Size Software®[7] to assess effects on power and timing of interim and final OS analyses.

Based on observations from ipilimumab trials and observations from MDX1106-03 study in lung cancer, key modeling assumptions are made as follows: a 4-months delayed separation of curves between docetaxel and nivolumab treatment groups, an exponential distribution for docetaxel (7 months median OS), a 18% 'cure' rate (long term survival) in the nivolumab treatment group, and a 7.9 months median OS for 'non-cured' nivolumab subjects. The piecewise mixture distribution for nivolumab has an overall 8.9 months median OS for all randomized nivolumab subjects. Based on the above piecewise mixture model assumptions, hazard ratio between nivolumab and docetaxel arm follows the following pattern: Months 0-4: HR=1; Month 6: HR=0.62; Month 12: HR= 0.51; Month 24: HR=0.28; Month 36: HR=0.13. Results from the simulations showed a reduction of power compared to the original design. In order to maintain 90% power for OS under the new model as described above, the design has been revised to have a later interim analysis for OS and increase the total number of OS events.

In the revised design, the final analysis of OS will be conducted when at least 231 deaths have been observed among 272 randomized subjects. Interim analysis of OS will be conducted when at least 196 deaths (85% of total deaths) have been observed. Given the observed accrual and the survival assumptions it is expected that the duration of the study from start of randomization to final analysis will be approximately 38 months (14 months of accrual + 24 months of follow-up). The expected duration until interim analysis is approximately 26 months after start of randomization.

Under the above-described model assumptions and revised design, the average overall HR at interim and final OS analysis will be 0.74 and 0.66 respectively. Power at interim and final OS analysis will be 55% and 90% respectively.

Additional details for side to side comparison between original and revised design are included in Table 5-1.

Table 5-1: Design of the CA209-017 Study: revised vs. original

	Original Design	Revised Design
Primary endpoints (alpha)	ORR (0.01), OS (0.04)	OS (0.05)
N randomized / Randomization	n=264 (planned)/ 1:1 (nivo: docetaxel)	n=272 (actual)/ 1:1 (nivo: docetaxel)
Target ORR effect (≥ 90% power)	10% vs. 35%	ORR is a secondary endpoint
Timing of ORR	264 subjects randomized + 6 months and ≥65% OS events	At time of OS IA analysis
Target OS effect (90% power)	Docetaxel: 7 mo mOS Nivolumab: 11.4 mo mOS Proportional hazards: HR=0.61 Exponential distribution for both treatment groups	Exponential distribution for docetaxel (7 mo mOS) Piecewise mixture distribution for nivolumab (8.9 mo mOS[a]) Non-proportional hazards[b] based on: 4 mo delayed separation of curves 18% 'cure' rate for nivolumab 7.9 mo mOS for 'non-cured'
Timing of OS IA[c]	≥65% OS events at the same time as ORR (LPLV = 20 months)	85% OS events, not linked to ORR (LPLV = 26 months)
Final OS	189 OS events (LPLV = 26 months)	231 OS events (LPLV = 38 months)

[a] Overall median OS for nivolumab treatment group maintained at a fixed number similar to median OS observed in the squamous NSCLC population from the Phase I study MDX1106-03f (median OS :9.2 months as per September 17 2013 database lock), via assumed hazard for non-cures

[b] Months 0-4: HR=1; Month 6: HR=0.62; Month 12: HR= 0.51; Month 24: HR=0.28, Month 36: HR=0.13

[c] O'Brien-Fleming alpha spending function for formal interim and final OS analyses

The stopping boundaries at interim and final analyses will be derived based on the number of deaths using O'Brien and Fleming alpha spending function (see Table 5-2).

Table 5-2: Key Parameters in Statistical Design

Analysis	Timing	Nominal significance level	Probability for declaring superiority under H_1/H_0
Interim analysis for superiority	196 deaths at 26 months (14 months accrual + 12 months of follow-up)	Observed p-value < 0.030[a]	55% / 3%
Final analysis for superiority	231 deaths at 38 months (14 months accrual + 24 months of follow-up)of follow-up)	Observed p-value < 0.041	35% / 2%
Total probability to declare superiority			90% / 5%

[a] Using O'Brien and Fleming alpha spending function in case exact 196 OS deaths are observed at the interim OS analysis.

The secondary endpoints investigator-assessed ORR and PFS will be tested hierarchically (see details in Section 7.5.3). Assuming ORR on docetaxel and nivolumab are 10% and 35%, respectively, 272 subjects will provide more than 90% power to detect a response rate difference of 20% with a two-sided type I error of 5% at the time of the final analysis of OS (after 231 deaths).

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

See Core Safety SAP.

6.2 Treatment Regimens

The treatment group "**as randomized"** will be retrieved from the IVRS system

- Arm A: Experimental Arm (monotherapy) nivolumab.
- Arm B: Control arm docetaxel.

The treatment group "**as treated**" will be the same as the arm randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 Populations for Analyses

- **All enrolled subjects**: All subjects who signed an informed consent form and were registered into the IVRS. Analyses of the patients enrolled into the study but not randomized and the reason for not being randomized will be performed on the data set of all enrolled subjects.

- **All randomized subjects**: All subjects who were randomized to any treatment group in the study. This is the primary dataset for analyses of demography, protocol deviations, baseline characteristics, efficacy, outcome research and PD-L1expression.
- **All treated subjects**: All subjects who received at least one dose of nivolumab or docetaxel. This is the primary dataset for dosing and safety.
- **Response evaluable subjects**: randomized subjects whose change in the sum of diameters of target lesions was assessed (ie.: target lesion measurements were made at baseline and at at least one on-study tumor assessment).
- **All PD-L1 Tested subjects**: All subjects, randomized or not, who had a tumor biopsy specimen available for PD-L1 expression testing. This includes both randomized and screen failure subjects.
- **All randomized subjects with quantifiable PD-L1 expression at baseline:** see definition of baseline and quantifiable PD-L1 expression in Section 4.2.3.
- **Immunogenicity subjects**: See Core Safety SAP.

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum and maximum values.

Time to event distribution (e.g. progression free survival, overall survival and duration of response) will be estimated using Kaplan Meier techniques.

Median survival time along with 95% CI will be constructed based on a log-log transformed CI for the survivor function S(t) [8,9]. Rates at fixed timepoints (e.g. OS at 6 months) will be derived from the Kaplan Meier estimate and corresponding confidence interval will be derived based on Greenwood formula for variance derivation and on log-log transformation applied on the survivor function S(t)[10].

Unless otherwise specified, a stratified log-rank test will be performed to test the comparison between time to event distributions (e.g. PFS and OS). Stratification factors will be prior use of paclitaxel vs. other prior treatment, and region as entered into the IVRS.

Unless otherwise specified, the stratified hazard ratio between 2 treatment groups along with CI will be obtained by fitting a stratified Cox model with the treatment group variable as unique covariate.

The difference in rates between the two treatment arms along with their two-sided 95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting[11], adjusting for the stratification factors:

$$\hat{\theta} = \frac{\sum_i w_i \hat{\theta}_i}{\sum_i w_i} \sim N\left[\theta, \frac{\sum_i w_i^2 \left[\frac{p_{ix}(1-p_{ix})}{n_{ix}-1} + \frac{p_{iy}(1-p_{iy})}{n_{iy}-1}\right]}{\left(\sum_i w_i\right)^2}\right]$$

where $\hat{\theta} = p_{ix} - p_{iy}$ is the rate difference of the ith stratum, $w_i = \frac{n_{ix} n_{iy}}{n_{ix} + n_{iy}}$, and n_{ix} and n_{iy} are the number of subjects randomized to treatments x and y, respectively, in the ith stratum.

Stratification factors will be same as above. Associated odds-ratio will be derived.

P-values from sensitivity analyses are for descriptive purpose only and there will be no multiplicity adjustment for these analyses.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site and per month for all enrolled subjects. Randomization date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

7.2.2 Relevant Protocol Deviations

The relevant Protocol Deviations will be summarized for all randomized subjects, by treatment group and overall. The following programmable deviations from inclusion and exclusion criteria will be considered as relevant protocol deviations. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

At entrance:

- Subjects with any NSCLC histology other than squamous cell.
- Subject with baseline ECOG PS > 1.
- Subjects without measurable disease at baseline.
- Subjects who received prior treatment with docetaxel.

On-Study:

- Subjects receiving concurrent anti-cancer therapy (defined as chemotherapy, hormonal immunotherapy, radiation therapy, standard or investigational agents for treatment of NSCLC).
- Subject treated differently as randomized (subjects who received the wrong treatment, excluding the never treated).

A by subject listing will be produced.

7.3 Study Population

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized. This analysis will be performed only on the all randomized population only.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated.

A subject listing for all randomized subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized.

7.3.2 Demographics and Other Baseline Characteristics

Descriptive statistics will be summarized the following baseline characteristics for all randomized subjects by treatment group as randomized. All baseline presentations will identify subjects with missing measurements.

- Age (descriptive statistics)
- Age (< 65, ≥ 65 - <75, ≥ 75, ≥ 65).
- Gender, Race/Ethnicity, Region.
- ECOG PS, Weight
- Smoking Status (Yes/No/Unknown).
- Disease Stage.
- Time from initial disease diagnosis to randomization (< 1 year, 1 - < 2 year, 2 - < 3 year, 3 - < 4 year, 4 - < 5 year, ≥ 5 year).
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target Lesions (Investigator Tumor Assessments at Baseline): presence of target lesions, site of target lesion, sum of reference diameters of target lesions.
- CNS metastases (yes/no).

7.3.3 Medical history- Concurrent diseases

General medical history will be listed by subject and pretreatment events will be tabulated.

7.3.4 Prior therapy agents

The following (source CRF) will be summarized by treatment group as randomized:

Prior anti-cancer therapy:

- Number of subjects by type of most recent prior platinum therapy received (cisplatin vs. carboplatin).
- Prior paclitaxel (yes/no).
- Prior maintenance therapy (yes/no).
- Best response to most recent prior regimen (CR/PR vs. SD vs. PD).
- Time from completion of most recent prior regimen to randomization (< 3, 3 - 6, > 6 months).
- Setting of prior systemic therapy regimen received (adjuvant, metastatic disease, neo-adjuvant Time from completion of prior adjuvant therapy to randomization (subjects who received prior adjuvant therapy), (< 6 months and ≥ 6 months).
- Prior surgery related to cancer (yes or no).
- Prior radiotherapy (yes or no).
- Prior systemic therapy classified by therapeutic class and generic name.

Other Prior therapy:

- Prior/current non-study medication classified by anatomic and therapeutic classes.

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline examinations

Subjects with abnormal baseline physical examination will be tabulated by examination criteria and by treatment group.

7.3.6 Discrepancies Between IVRS and CRF stratification factors

Summary tables (cross-tabulations) by treatment group as randomized for stratification factor will be provided to show any discrepancies between what was reported through IVRS vs. CRF data (baseline).

- Prior chemotherapy: Prior paclitaxel vs. other prior treatment.
- Note: Region factor is similarly defined in CRF and IVRS.

7.4 Extent of Exposure

Analyses in this section will be performed in all treated subjects by treatment group as treated.

7.4.1 Administration of study therapy

The following parameters will be summarized (descriptive statistics) by treatment group:

- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%.
- Number of doses received (summary statistics).

- Cumulative dose.

Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of dosing of study medication (record of study medication, infusion details, dose change) and a listing of batch number will be also provided.

Below table summarizes the key parameters used to calculate dosing data.

Table 7.4.1-1: Administration of study therapy: definition of parameters

	Nivolumab	Docetaxel
Dosing schedule per protocol	3mg/kg every 2 weeks	75mg/ m² every 3 weeks
Dose	*Dose (mg/kg)* is defined as Total Dose administered (mg) / Most recent weight (kg). Dose administered in mg at each dosing date and weight are collected on the CRF.	*Dose (mg/m²)* is defined as Total Dose administered (mg) / Most recent BSA. Dose administered in mg at each dosing date and BSA (computed using recent weight and bsl height) are collected on the CRF.
Cumulative Dose	*Cum dose (mg/kg) is* sum of the doses (mg/kg) administered to a subject during the treatment period.	*Cum dose (mg/m²) is* sum of the doses (mg/m²) administered to a subject during the treatment period.
Relative dose intensity (%)	Cum dose (mg/kg) / [(Last dose date - Start dose date + 14) x 3 / 14] x 100	Cum dose (mg/m²) / [(Last dose date - Start dose date + 21) x 75 / 21] x 100
Duration of treatment	Last dose date - Start dose date +1	Last dose date - Start dose date +1

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose delays

A dose will be considered as actually delayed if the delay is exceeding 3 days (i.e., greater than or equal to 4 days from scheduled dosing date) for both nivolumab and docetaxel. Subjects may be dosed with nivolumab no less than 12 days from the previous dose or 19 days for docetaxel.

It is defined as (duration of previous cycle in days - 14) for nivolumab or - 21 for docetaxel. Dose delays will be divided into following categories: on-time, 4-7 days, 8-14 days, 15-42, > 42 days. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of dose delayed per subject, Length of Delay and Reason for Dose Delay.
- Number of subject with at least one dose infusion interrupted along with reason for the interruptions and number of infusions interrupted per subject.

7.4.2.2 Infusion Modification

Each nivolumab or docetaxel infusion can be interrupted and/or the iv infusion rate can be reduced. This information will be retrieved from CRF dosing pages.
The following parameters will be summarized by treatment group:

- Number of subject with at least one dose infusion interrupted along with reason for the interruptions and number of infusions interrupted per subject.
- Number of subjects with at least one infusion with iv rate reduced along with the reason of the rate reduction.

7.4.2.3 Dose Reductions

There will be no dose escalations or reductions of nivolumab allowed.

Dose of Docetaxel may be modified for toxicity.

Dose levels of docetaxel are defined in the protocol as follows:

- Dose level 0. 75mg/m²
- Dose level -1. 55mg/m²
- Dose level -2. 35mg/m²

For any cycle (excluding Cycle 1), it will be defined as a dose reduction if the observed dose level (based on calculated administered dose) is below the dose level of the previously administered dose. Dose ranges for dose levels of docetaxel are defined in Table 7.4.2.3-1.

Table 7.4.2.3-1: Calculated Dose Ranges and Related Dose Levels of Docetaxel

Dose Range (mg/m²)	Dose Level
≥ 65	Level 0
≥ 45 – < 65	Level -1
< 65	Level -2

The reason for dose reduction as reported by the investigator will be tabulated for all instances of dose reduction based on the Dose Change CRF page. A category 'Unknown' will be defined for all reductions with no reason reported by the investigator.

The following will be summarized for docetaxel arm only:

- Number and percentage of subjects with at least one dose reduction and reason of the dose reduction, number and percentage of subjects with a dose reduction to dose level -1, number and percentage of subjects with a dose reduction to dose level -2.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary tables will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term).

A by-subject listing will accompany the table.

7.5 Efficacy

7.5.1 OS

7.5.1.1 Primary analysis of OS

The distribution of OS will be compared in two randomized arms at the interim and final analyses via a two-sided, log-rank test stratified (per IVRS) by prior use of paclitaxel vs. other prior treatment, and region (US vs. Europe vs. Rest of World).

The hazard ratio (HR) and the corresponding 100(1-α)% CI (adjusted for the interim) will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate.

The OS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product-limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t).

Survival rates at 6, 12, 18, 24, 36, 48 months and at 5 year will also be estimated using KM estimates on the OS curve for each randomized arm. Minimum follow-up must be ≥ timepoint to generate the rate. Associated two-sided 95% CIs will be calculated using the Greenwood's formula for variance derivation and on log-log transformation applied on the survivor function S(t).

The status of subjects who are censored in the OS Kaplan-Meier analysis will be tabulated for each treatment group using following categories:

- on-study (on-treatmentor in follow-up).
- off-study: (lost to follow-up, withdraw consent, etc.).

To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential nonconstant treatment effect. In that case, additional exploratory analyses may be performed.

7.5.1.2 OS sensitivity analyses

The following OS sensitivity analyses will be performed:

- OS will be compared between treatment groups using a two-sided α (adjusted for the interim) unstratified log-rank test.
- OS will be compared between treatment groups using the strata as determined at baseline (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

- OS will be compared between treatment groups using a two-sided α (adjusted for the interim) stratified log-rank test in the all treated Subjects population, using arm as randomized. This analysis will be performed only if the proportion of randomized but never treated subjects exceeds 10%.

Estimate of the hazard ratio, its two sided 100(1-α)% CI (adjusted for the interim) and p-value will be presented.

7.5.1.3 Consistency of treatment effect on OS in subsets

To assess consistency of treatment effects in different subsets, a "forest" plot of the OS unstratified hazard ratio (and 95% CI) will be produced for the following subgroups:

- Prior paclitaxel vs. other prior treatment (per CRF).
- Region (US/Canada , Europe , Rest of World).
- Age categorization 1 (< 65, ≥ 65)
- Age Categorization 2 (<75, ≥ 75)
- Age Categorization 3 (<65, ≥65-<75, ≥ 75).
- Gender (Male , Female).
- Race (White, African American, Asian, Other).
- ECOG PS (0 vs. 1).
- Stage (IIIB vs. IV).
- Type of prior Pt regimen (cisplatin vs. carboplatin).
- MET receptor status (positive vs. negative vs. unknown).
- Time from diagnosis to start of treatment (< 1 year (yes vs. other)).
- Time from completion of most recent regimen (< 3 mos, 3-6 mos, and > 6 mos).
- CNS metastases (yes/no)
- Smoking status (yes vs other (no or unknown)).

If subset category has less than 10 subjects per treatment group, HR will not be computed/displayed. Number of events and median OS along with 95% CI) will be displayed for each treatment group.

7.5.1.4 Multivariate OS analysis

A multivariate stratified (by Paclitaxel vs. other prior chemo (per CRF) and region (US/Canada vs. Europe vs. Rest of World)) Cox model will be fitted to assess the treatment effect on OS when adjusted for potential prognostic factors. The following prognostic factors (source: CRF) will be included in the model in addition to treatment group variable:

- Time from diagnosis to start of treatment (< 1 year (yes vs. other)).
- Age categorization (< 65, ≥ 65).
- Gender (Male vs. Female).
- Baseline ECOG PS (0 vs. 1).

- Stage (IIIB vs. IV)
- Smoking status (yes vs. other)

HR and 95% CI will be provided for treatment variable and all covariates. Descriptive p-values will be provided.

7.5.1.5 Subject Follow-up for OS

The minimum follow-up will be reported. The minimum follow-up is defined as the time interval between the last patient's randomization date and the clinical cutoff date.

The extent of follow-up defined as the time between randomization date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all subjects randomized.

The currentness of follow-up, defined as the time between last OS contact (i.e., last known date alive or death date) and data cut-off date, will be summarized by treatment group. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-3 months, 3-6 months, 6-9 months, 9-12 months and ≥ 12 months.

7.5.1.6 Follow-Up Therapy

The following information pertaining to subsequent therapies will be summarized:

Number and percentage of subjects receiving subsequent therapies including:

- Chemotherapy by drug name.
- Immunotherapy (anti-PD1 agents, anti-CTLA4 agents and others, by drug name).
- Tyrosine kinase inhibitor by drug name.
- Other investigational agent by drug name.
- Surgery.
- Radiotherapy.
- Any combination of the above.

A subject listing of follow-up therapy will be produced for subjects who had any subsequent therapy.

7.5.1.7 Analysis of survival by tumor response

Survival by response category as assessed by the investigator will be analyzed by treatment group using the landmark method[12]. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time.

This will assess whether survival from the landmark depends on the subject's BOR based response status at the landmark. Subjects who go off protocol (e.g. subjects who die) before the time of landmark will be excluded from the analysis.

The survival curves from Week 9, Month 4, Month 6, Month 8, Month 12, by response status, for each randomized group will be produced using the KM product-limit method. Two sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function S(t).

7.5.2 Secondary Efficacy Endpoint Analyses

7.5.2.1 Investigator-assessed ORR

Investigator-assessed BOR will be summarized by response category for each treatment group. ORR will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology and adjusted by the same stratification factors as in primary analysis of OS. A by subject listing of BOR and Tumor Measurements will be provided.

The stratified (source: IVRS) odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a two-sided, 5% α level.

To assess consistency of treatment effect on ORR in different subsets, ORR will be computed across the same subsets as defined in the OS analysis.

If one stratification variable at IVRS and at baseline (CRF) disagrees for at least 10% of the randomized subjects, similar analysis of ORR as primary analysis will be performed using the strata as determined at baseline.

Summary statistics of time to objective response will be provided for each treatment group for subjects who achieve PR or CR, as assessed by the investigator.

To assess further tumor response kinetics, time to response will be analyzed using the KM methodology, for all randomized subjects. Kaplan-Meier curve will represent the cumulative rate of response over time. For the non-responders, time to response will be censored at the maximum time of response + 1day of all subjects in their respective treatment group. Cumulative Response Rates will be tabulated for Week 9, Month 4, 6, 8, and 12, and overall Response Rate will be provided for each treatment group.

Duration of response in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Median values along with two-sided 95% CI will be calculated.

Duration of stable disease will be estimated using Kaplan-Meier (KM) product-limit method. for subjects with SD as BOR. Two-sided, 95% confidence intervals for median duration of SD will be computed.

The following subject-level graphics will also be provided by treatment group as randomized:

- For the responders only, time courses of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response evaluable subjects, a waterfall plot showing the best reduction in target lesion will be produced.

7.5.2.2 PFS

Primary analysis of PFS

PFS will be compared between the two randomized groups using a two-sided, log-rank test stratified by prior use of paclitaxel vs. other prior treatment, and region (US vs. Europe vs. Rest of World).

HR and corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazards model using randomized arm as a single covariate. The PFS curves for each treatment group will be estimated using the KM product-limit method. Two sided, 95% confidence intervals for median PFS will be constructed based on a log-log transformed CI for the survivor function S(t).

The source of PFS event (death vs. progression) will be summarized by treatment group. The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each treatment group using following categories:

- Never treated
- On-study (on treatment or progression-free in follow-up).
- Off-study: (lost to follow-up, withdraw consent other).
- Received subsequent anti-cancer therapy.

To assess consistency of treatment effect on PFS in different subsets, a “forest” plot of the PFS unstratified hazard ratio (and 95% CI) will be produced for the same variable as in the OS analysis.

PFS rates at 6 months will be estimated using KM estimates on the PFS curve. PFS rates at 12, 18, 24, 36, 48 months and at 5 year may also be estimated depending on whether minimum follow-up will be longer than or equal to timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

Sensitivity analyses of PFS

Sensitivity analyses of PFS will also be performed using modifications of PFS primary definition, as described below. Median PFS, HR (95% CIs), p -value from the log-rank test will be computed as in the primary PFS analysis

- PFS will be compared between treatment groups *using the strata as determined at baseline* (CRF source). This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects

- *PFS accounting for assessment after subsequent therapy* subjects will be defined similarly to the primary definition except that events (progression or death) and tumor assessments that occurred after subsequent anticancer therapy will be taken into account. A Kaplan-Meier plot will be produced.

- *PFS accounting for missing tumor assessment prior to PFS event (progression or death)*. This analysis will be performed only if at least 20% of events have missing prior tumor assessment.. It will apply the following restriction to the primary definition: If the elapsed time between the PFS event (progression or death) and the last on-study tumor assessment immediately prior to the event (or randomization date if no on-study scan) is two or more missed visits (more than 12 weeks + 10 days), the subject will be censored at his last tumor assessment prior to the PFS event (or randomization date if no on-study scan). A Kaplan-Meier plot will be produced.
- PFS *accounting for assessment after on-treatment palliative radiotherapy on bone or CNS non-target lesions*. This analysis is similar to the primary analysis except that no censoring will occur for on-treatment palliative radiotherapy. A Kaplan-Meier plot will be produced.

7.5.3 Hierarchy for Key Secondary Efficacy Endpoints

In order to preserve an experimental-wise type I error rate at 5%, a pre-planned hierarchy for key secondary endpoints will be applied when interpreting the statistical significance of treatment comparisons. The hierarchical ordering of the key secondary endpoints is as follows:

Objective Response Rate

Progression-Free Survival

The statistical testing will be carried out using the following sequential procedure:

1) The primary endpoint of OS will be tested first.

If the p-value of OS is not statistically significant against nominal significance level either at interim or final analysis, then no further statistical testing regarding the secondary endpoints will be conducted. However estimates along with their 95% CI will be provided for those (i.e. medians and HR, rates, odds ratio and rate difference), at final OS analysis

If the p-value of OS is statistically significant against nominal significance level either at interim or final analysis, the secondary endpoint with the highest ranking in the hierarchy will be tested (ORR in this case). If the p-value of ORR is statistically significant at 5% level, the second highest ranking endpoint in the hierarchy will be tested (PFS in this case) and the p-value of PFS will be provided. If the p-value of ORR is not statistically significant at 5% level, then no further statistical testing regarding the other secondary endpoint (i.e., PFS) will be conducted. Estimates (medians and HR) and their 95% CI will be provided for PFS regardless of the outcome of ORR testing.

7.5.4 Interim Analysis

A formal interim analysis for superiority of OS in subjects who were randomized to nivolumab vs. subjects who were randomized to docetaxel will be performed on all randomized subjects when at least 196 deaths have been observed (approximately 85% (196/231) of the total number of deaths required for the final analysis).

This OS comparison will be tested using the interim monitoring feature of EAST software based on a generalization of the Lan-DeMets error spending function approach using an O'Brien-Fleming stopping boundary to reject H_0, controlling for a two-sided overall α of 5%. For example, if exactly 196 deaths are in the locked database at the interim analysis, H_0 would be rejected if the p-value from the log-rank test is $p < 0.03$. If the number of deaths is not exactly 196 at the time of the interim analysis, the nominal critical point and value of both the interim and final analysis will be calculated based upon the observed information fraction.

The DMC will review the safety and efficacy data from the interim analyses and will determine if the study should continue or should be stopped. If the trial is stopped for superiority at the interim, the p-value will be considered as the final OS result. All secondary endpoint analyses will be tested at that time. The p-values from these analyses will be considered as the final results. See Section 7.5.3 for type I error control for secondary endpoints

If the study continues beyond the interim analysis and exactly 231 deaths are in the locked database at the final analysis, H_0 would be rejected if the p-value from the log-rank test is $p < 0.041$. All events in the database at the time of the lock will be used. If number of final events exceeds the number specified per protocol (231 deaths), final boundary will not be recalculated using updated information fraction at interim.

7.6 Safety

7.6.1 Deaths

See Core Safety SAP.

7.6.2 Serious Adverse Events

See Core Safety SAP.

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See Core Safety SAP.

7.6.4 Adverse Events Leading to Dose Delay of Study Therapy

See Core Safety SAP.

7.6.5 Adverse Events

See Core Safety SAP.

7.6.6 Multiple Events

See Core Safety SAP.

7.6.7 Select Adverse Events

See Core Safety SAP.

7.6.8 Clinical laboratory evaluations

The analysis population for each laboratory test is restricted to treated subjects who underwent that laboratory test.

7.6.8.1 Hematology

See Core Safety SAP.

7.6.8.2 Serum Chemistry

See Core Safety SAP.

7.6.9 Vital Signs and Pulse Oximetry

See Core Safety SAP.

7.6.10 Immunogenicity Analysis

Nivolumab arm only. See Core Safety SAP

7.6.11 Pregnancy

See Core Safety SAP.

7.6.12 Clinical Safety Program (CSP)

See Core Safety SAP.

7.7 Biomarker Analyses

Analyses of PD-L1 will include:

- Examine the distribution of PD-L1 expression
- Assess potential association between PD-L1 PD-L1 status and efficacy measures
- Evaluate the potential predictive relationship of the PD-L1 status and efficacy measures
- Test performance statistics such as sensitivity, specificity, Positive Predictive Value and Negative Predictive Value
- Assess potential association between PD-L1 status and select AEs

7.7.1 Distribution of Baseline PD-L1 expression

The following descriptive statistics analyses of PD-L1 expression and PD-L1 status at baseline will be performed:

- Listing of all PD-L1 IHC data, all PD-L1 tested subjects
- Summary of tumor specimen acquisition and characteristics, all randomized subjects.
- Cumulative distribution plot of baseline PD-L1 expression versus population percentile by treatment group and overall, all randomized subjects with quantifiable PD-L1 expression at baseline
- Waterfall plots of individual PD-L1 expression at baseline by treatment group, all randomized subjects with quantifiable PD-L1 expression at baseline

Frequency of PD-L1 Status at baseline, by treatment group for select subgroups and overall, all randomized subjects. Selected subgroups will be the same as subgroup analysis for primary endpoint.

7.7.2 Association between PD-L1 status at baseline and efficacy measures

Evaluation of associations between PD-L1 PD-L1 status (using the 3 pre-defined cut-off values) and efficacy measures, analyses will be based on all randomized subjects if not otherwise specified.

Analyses for OS endpoint:

- OS curves by treatment group for each PD-L1 status at baseline will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS will be computed.
- Forest plot of Hazard Ratios with 95% CIs for treatment effect by PD-L1 status at baseline

Analyses for PFS endpoint:

- PFS curves by treatment group for each PD-L1 status at baseline will be estimated using the Kaplan-Meier productlimit method. Two-sided, 95% confidence intervals for median PFS will be computed.
- Forest plot of Hazard Ratios with 95% CIs for treatment effect by PD-L1 status at baseline

Analyses for ORR (BOR):

- Frequency and percentage of BOR will be summarized by PD-L1 status at baseline for each treatment group. ORR will be computed by PD-L1 status at baseline for each treatment group along with exact 95% CIs using the Clopper-Pearson method.
- Box plots of PD-L1 expression at baseline versus Response Status by treatment group will be generated using all randomized subjects with quantifiable PD-L1 expression at baseline

7.7.3 Predictive relationship of PD-L1 status for efficacy measures

Evaluation of the potential predictive relationship of PD-L1 status (using the 3 pre-defined cut-off values) for efficacy measures will be performed on all randomized subjects with quantifiable PD-L1 expression at baseline subjects

Analyses for OS endpoint:

A Cox proportional hazards regression model will be fitted for OS with treatment, PD-L1 status (Positive vs Negative), and treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Hazard ratio of treatment vs. control and its associated 95% CI for each of the PD-L1 status subgroup
- Hazard ratio PD-L1 positive vs. negative and its associated 95% CI within each treatment group.

Analyses for PFS endpoint:

A Cox proportional hazards regression model will be fitted for PFS with treatment, PD-L1 status and treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Hazard ratio of treatment vs. control and its associated 95% CI for each of the PD-L1 status subgroup
- Hazard ratio PD-L1 positive vs. negative and its associated 95% CI within each treatment group.

Analyses for ORR endpoint:

A logistic regression model will be fitted for response (yes=CR or PR, No=SD or PD or unknown) with treatment, PD-L1 and the treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Odds ratio of treatment vs. control and its associated 95% CI will be reported for each of the PD-L1 status subgroup
- Odds ratio of PD-L1 positive vs. negative and its associated 95% CI will be reported for each treatment group

7.7.4 Performance statistics for PD-L1 status vs. efficacy measures

Evaluation of the test performance statistics of PD-L1 status vs. response status will be performed on all randomized subjects with quantifiable PD-L1 expression at baseline.

- 2 by 2 contingency table of PD-L1 status by response status (yes=CR or PR; No=SD or PD or unknown). Sensitivity, specificity, Positive Predictive Value and Negative Predictive Value will be reported along with the contingency table

7.7.5 Association of Select AE and PD-L1 status at baseline,

Population for the analyses will be all treated subjects

Select AEs will be summarized (any grade, grade 3-4, grade 5) by PD-L1 status at baseline using a 1% cutoff value for each treatment group.

7.8 Outcomes Research Analyses

The outcome research analyses will be performed using all randomized subjects.

7.8.1 LCSS questionnaire

LCSS questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (i.e., the number of subjects still on treatment or in follow-up), will be calculated and summarized at each assessment point.

Baseline and change from baseline of the average symptom burden index score at each assessment point will be summarized using descriptive statistics (N, mean, median, SD, 25th and 75th percentiles) by treatment group, as randomized. The summary at baseline and at each time point is based on all randomized subjects with a baseline measurement. The change from baseline analysis will only include subjects who have an assessment at baseline and at the assessment point.

Disease-related symptom improvement rate by Week 12 and its corresponding 95% exact CI will be calculated for each treatment group, based on all randomized subjects, using the Clopper-Pearson method.

7.8.2 EQ-5D questionnaire

Subject's overall health state on a visual analog scale (EQ-VAS) at each assessment time point will be summarized using descriptive statistics (N, mean, SD, median, 25th and 75th percentiles) by treatment group, as randomized.

Proportion of subjects reporting problems for the 5 EQ-5D dimensions at each assessment time point will be summarized by level of problem and by treatment group, as randomized. Percentages will be based on number subjects assessed at assessment time point.

A by-subject listing of EQ-5D with the problem levels for each of the 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression), health state (5 dimensions digits combined in a 5-digit number) and EQ-VAS will be provided.

Results of EQ5D-Index will be presented separately and will be described in the GHEOR SAP.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[13]. Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in BMS Non-Study Medication Domain Requirements Specification[14].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known alive date and the maximum will be considered as the death date.

- If the month or the year is missing, the death date will be imputed as the last known alive date.
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known alive date.

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day.
- If the day and month are missing or a date is completely missing, it will be considered as missing.
- In case, the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions will be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years:

1 month = 30.4375 days and 1 year = 365.25 days

Duration (e.g. time from first diagnosis of RCC to first dosing date, duration response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

Safety conventions from Programming may be summarized separately in an appendix.

9 CONTENT OF REPORTS

All analyses describe in this SAP will be included in the final Clinical Study Report. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 REFERENCES

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11 DOCUMENT HISTORY

Table 11-1: Document History

Version Number	Author(s)	Description
1.0	Christine Baudelet	Initial version- 09-Aug-2013
2.0	Christine Baudelet	04 June 2014 • SAP updated to reflect change in primary endoint per Protocol V03. OS as the sole primary endpoint and ORR per investigator as the first secondary endpoint in the hierarchy. IRC analyses removed. • OS modeling for Nivolumab updated to account for a delayed effect onset of benefit and long term survival. Timing of interim and final OS analysis revised • OS sensitivity analysis added on all treated Subjects population • Minimum follow-up definition added • ORR analysis in subsets and difference in ORR added • Analysis of PFS rates at selected timepoints added • PFS sensitivity analysis not censoring for on-treatment palliative radiotherapy added • Analysis of duration of stable disease added • PD-L1 analysis revised • Summary table added for number of subjects randomized but not treated • Age category >=65 and smoking category unknown added • Tabulation for pretreatment events added • Clarification of method for confidence intervals for survival median and rates • Clarification of on-treatment palliative radiotherapy impact on objective response evaluation • PK summary table and listing removed

NEW or MODIFIED **STATISTICAL ANALYSIS PLAN** APPROVAL PAGE

Study Specific SAP for CA209-017

AN OPEN-LABEL RANDOMIZED PHASE III TRIAL OF NIVOLUMAB (BMS-936558) VERSUS DOCETAXEL IN PREVIOUSLY TREATED ADVANCED OR METASTATIC SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

Version 2.0

Prepared by:	Christine Baudelet		June 04, 2014
	Statistician	Signature	Date
	Brian Lestini		6/4/14
	Study Director	Signature	Date

Approved by:

■ Study-Specific SAP	Aparna Anderson		05 June 2014
	GBS Lead	Signature	Date
	David Feltquate		
	Medical Lead**	Signature	Date
☐ Study-Specific SAP (NIR)			
	NIR Study Director	Signature	Date
	TA Head of GHEOR, GPV&E, or Local/Regional HEOR	Signature	Date
	GBS Lead (if applicable)	Signature	Date
☐ Core or Integrated SAP			
	GBS Lead	Signature	Date
	Medical Lead	Signature	Date
	TA Head, GBS	Signature	Date
	Development Lead	Signature	Date
☐ Summary of Clinical Pharmacology			
	TA Head, CP&P	Signature	Date
	TA Head, GBS	Signature	Date
☐ DMCP Standard SAP			
	GBS Head of Early Development	Signature	Date
	VP, DMCP	Signature	Date

NEW or MODIFIED STATISTICAL ANALYSIS PLAN **APPROVAL PAGE**

Study Specific SAP for GA209-017

AN OPEN-LABEL RANDOMIZED PHASE iII TRIAL OF NIVOLUMAB (BMS-936568) VERSUS DOCETAXEL IN PREVIOUSLY TREATED ADVANCED OR METASTATIC SQUAMOUS CELL NON-SMALL CELL LUNG CANCER (NSCLC)

Version 2.0

Prepared by:	Christine Baudelet Statistician	Signature	June 04, 2014 Date
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