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Clinical Protocol CA209384

A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 3 mg/kg Every 2 Weeks vs Nivolumab 6 mg/kg Every 4 Weeks in Subjects with Previously Treated Advanced or Metastatic Non-small Cell Lung Cancer who Received 4 Months of Nivolumab at 3 mg/kg Every 2 Weeks

CheckMate 384: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 384

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Medical Monitor

Angelic Acevedo, MD

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	03-Nov-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209384

Protocol Title: A Dose Frequency Optimization, Phase IIIB/IV Trial of Nivolumab 3 mg/kg Every 2 Weeks vs Nivolumab 6 mg/kg Every 4 Weeks in Subjects with Previously Treated Advanced or Metastatic Non-small Cell Lung Cancer who Received 4 Months of Nivolumab at 3 mg/kg Every 2 Weeks

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Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab at 3 mg/kg every 2 weeks as a 30-minute (± 5 minutes) intravenous (IV) infusion or nivolumab 6 mg/kg every 4 weeks as a 30-minute (± 5 minutes) IV infusion until disease progression, unacceptable toxicity, or withdrawal of informed consent for up to 5 years.

Study Phase: 3b/4

Research Hypothesis: Progression-free survival (PFS) rate at 6 months and at 1 year after randomization in subjects receiving nivolumab 6 mg/kg every 4 weeks will be non-inferior to PFS rate in subjects receiving nivolumab 3 mg/kg every 2 weeks for the treatment of advanced/metastatic (Stage IIIb/IV) non-small cell lung cancer (NSCLC; non-Squamous [non-Sq] and Squamous [Sq]) who failed at least 1 prior platinum-based systemic therapy and receiving 4 months (16 weeks ± 2 weeks) of 3 mg/kg nivolumab every 2 weeks prior to enrollment.

Objectives: The coprimary objectives are to compare PFS rate at 6 months after randomization and PFS rate at 1 year after randomization, as measured by investigator-assessed response using Response Evaluation Criteria in Solid Tumor (RECIST) 1.1 criteria, of nivolumab 3 mg/kg every 2 weeks (Arm 1) and nivolumab 6 mg/kg every 4 weeks (Arm 2) in subjects with advanced/metastatic (Stage IIIb/IV) NSCLC (non-Sq and Sq).

The secondary objectives are:

- To compare PFS rate in Arms 1 and 2 at 1 year after randomization by tumor histology and by response before randomization
- To compare PFS rate at 2 years after randomization in Arms 1 and 2.
- To compare the overall survival (OS) rate at 1 year after randomization and up to 5 years after randomization in Arms 1 and 2, in all treated subjects, by tumor histology, and by response criteria before randomization
- To assess safety and tolerability of nivolumab, as measured by the incidence and severity of adverse events (AEs) and specific laboratory abnormalities, in all treated subjects, in Arms 1 and 2, by tumor histology and response before randomization

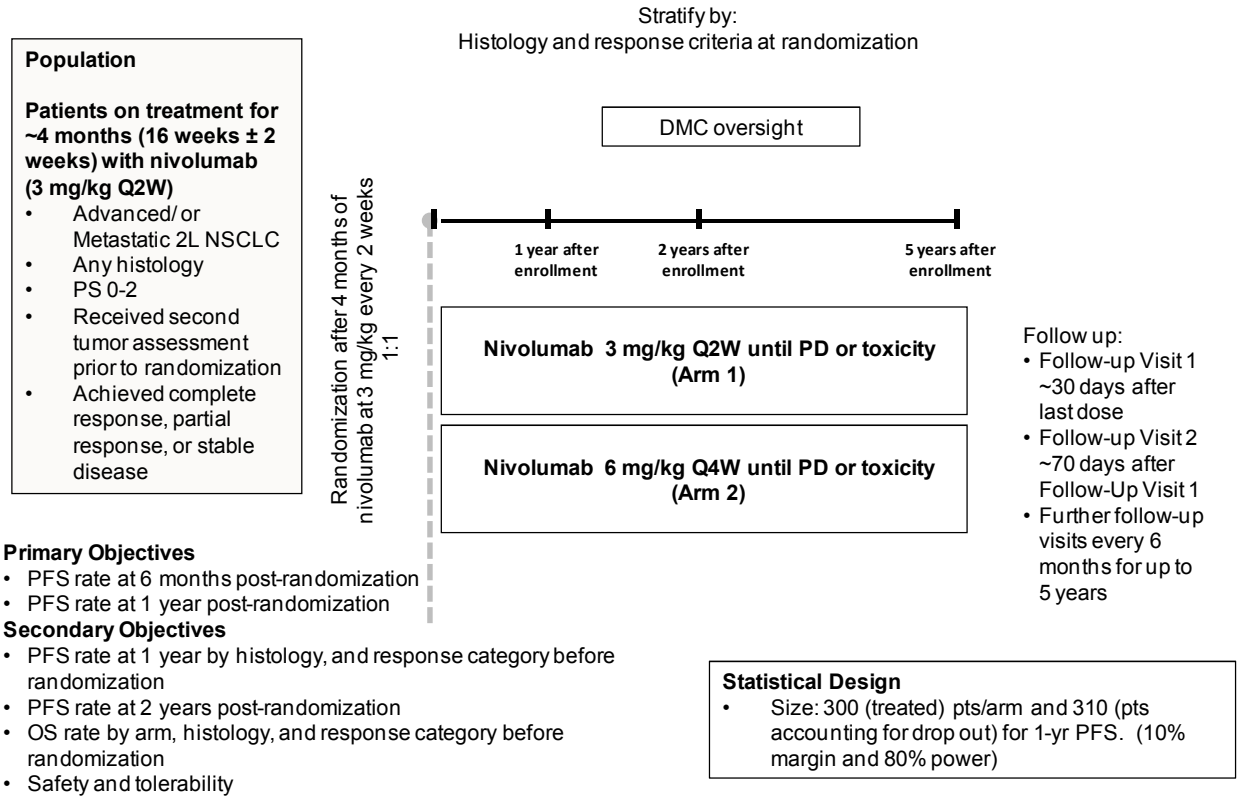
[redacted]

Study Design: Subjects will have received approximately 4 months (16 weeks ± 2 weeks) of nivolumab therapy at 3 mg/kg every 2 weeks and achieved a complete response (CR), partial response (PR), or stable disease (SD) as evidenced by a second tumor assessment prior to screening and enrollment. At enrollment, subjects will be randomized 1:1 to receive either 3 mg/kg every 2 weeks (Arm 1) or 6 mg/kg every 4 weeks (Arm 2). Randomization will be stratified by histology and response criteria at randomization (CR or PR vs SD). For subjects receiving

nivolumab 3 mg/kg every 2 weeks, each 14-day dosing period will constitute a cycle. For subjects receiving nivolumab 6 mg/kg every 4 weeks, each 28-day dosing period will constitute a cycle.

Subjects will continue treatment until disease progression or unacceptable toxicity for a maximum of 5 years from first randomized dose. The follow-up period begins when the decision to permanently discontinue a subject from study therapy is made (no further treatment or retreatment with nivolumab is anticipated).

Study Schematic



Study Population:

Key Inclusion Criteria:

a) Subjects with histologically or cytologically documented Sq- or non-SqNSCLC 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 chemoradiotherapy for locally advanced disease).

b) Subjects must have received and tolerated nivolumab 3 mg/kg every 2 weeks for approximately 4 months (16 weeks ± 2 weeks). Subjects may continue to receive pre-study nivolumab treatment during screening assessments. Subjects who receive nivolumab flat dosing are ineligible for this study.

c) Subjects must have at least 2 tumor assessments after the start of nivolumab and must demonstrate CR, PR, or SD to the pre-study nivolumab treatment on the latest scan within 28 days prior to randomization.

d) Subjects must have had measurable disease by CT or MRI per RECIST 1.1 criteria at the time of starting first dose of pre-study nivolumab treatment.

e) Subjects must have experienced disease progression or recurrence during or after at least 1 systemic platinum-based therapy for advanced or metastatic disease prior to starting the first dose of pre-study nivolumab.

   i) Each line of therapy should have been preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.

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

   iii) Subjects who received platinum-based 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.

   iv) Subjects with recurrent disease > 6 months after platinum-based adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum-based regimen given to treat the recurrence, are eligible.

   v) Subjects with a known activating epidermal growth factor receptors (EGFR) mutation or anaplastic lymphoma kinase (ALK) translocation are eligible if they have received an EGFR or ALK TKI in addition to a platinum-based chemotherapy

   vi) Experimental therapies when given as separate regimen are considered as separate line of therapy.

f) Eastern Cooperative Oncology Group (ECOG) PS 0-2

Key Exclusion Criteria

a) Subjects with carcinomatous meningitis

b) Subjects with untreated, symptomatic CNS metastases are excluded

c) Subjects with interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Subjects with chronic obstructive pulmonary disease whose disease is controlled at study entry are allowed.

Study Drug: includes both Investigational [Medicinal] Products (IP/IMP) and Non-investigational [Medicinal] Products (Non-IP/Non-IMP) as listed:

Study Drug for CA209384		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	100 mg (10 mg/mL)	IP

Study Assessments: Safety assessments will be conducted throughout the trial and during 100 days after the last dose of study treatment. The assessments are described in the Time and Events Schedule and should be monitored starting on Cycle 1 Day 1 until discontinuation from study therapy. National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 will be the criteria used to assess severity of AEs. Efficacy assessments will take place according to the Time and Events Table. 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 should be assessed by the investigator using RECIST 1.1.

Samples for pharmacokinetic (PK) assessments will be collected for all subjects receiving nivolumab. All time points are relative to the start of study drug administration.

The EQ-5D-3L comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety) and a visual analog rating scale. The responses to the EQ-5D-3L domains will be converted to health status index based on the European scoring algorithm.

Statistical Considerations:

Sample Size: The primary analyses evaluates the non-inferiority of post-randomization 6-months and 12-month milestone PFS rate of nivolumab 6 mg/kg Q4W versus the PFS rate of nivolumab 3 mg/kg Q2W in subjects with disease control (CR/PR/SD) after approximately 4 months (16 weeks ± 2 weeks) of nivolumab 3 mg/kg Q2W treatment. The non-inferiority margin of -10% was chosen for this study. Patients who achieved CR, PR, or SD will be randomized after 4 months (16 weeks ± 2 weeks) of nivolumab treatment. It is estimated that the 12-month milestone PFS rate post-randomization is 0.384 with 3 mg/kg Q2W and 6-month PFS rate post-randomization is 0.52.

The sample size was computed based on a cumulative hazard function which account for both progression and censoring distributions. Using cumulative hazard function and its relation with survival function, it is estimated that 600 patients, 300 in each arm, will provide 80% power for the lower bound of a 95.3% one-sided confidence interval above -10% at the 12-month milestone and the lower bound of a 99.1% confidence interval above -10% at 6 months if PFS rates of the 2 arms are assumed to be equal. The experiment-wise error rate is maintained at one-sided 5% level.

To account for those who are randomized but not receiving treatment, 310 per arm will be randomized. With a 15% screen failure rate, approximately 730 subjects will be screened to achieve approximately 620 randomized subjects.

Endpoints: Primary Endpoints: The coprimary objectives of this trial will be assessed by PFS rate at 6 months after randomization and PFS rate at 1 year after randomization. PFS is defined as the time from the date of randomization to the date of first documented tumor progression determined by the investigator or death, whichever is earlier. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. PFS rate at 6 months is the rate from Kaplan-Meier estimate 6 months after randomization; PFS rate at 1 year is the rate from Kaplan-Meier estimate at 1 year after randomization.

Secondary objectives will be assessed by:

- PFS rate at 1 year after randomization by tumor histology and by response criteria
- PFS rate at 2 years after randomization
- OS rate at 1 year and OS up to 5 years by arm, histology, and response status at randomization. OS is defined as time from the date of randomization to the date of death. Subjects who did not die by the end of the study will be censored at the last known date alive. OS rate at 1 year is the rate from Kaplan-Meier (KM) estimated at one year after randomization.
- Safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities

[redacted]

Analyses: Efficacy analyses: PFS will be summarized by Kaplan-Meier (KM) product-limit method and confidence interval for hazard ratio will be produced from a stratified (by tumor histology and response category) proportional hazard model. Median values of PFS, along with one-sided 95% CI using Brookmeyer and Crowley method, will be calculated. The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each dose regimen.

The 95% one-sided confidence intervals for PFS rates at 6 and 12 months will be calculated using the Greenwood formula for each dose regimen and difference between dose regimens.

For the 6-month analysis, the 99.1% one-sided confidence interval around the difference in PFS rates between Q2W dose regimen and the Q4W regimen will be generated. If the lower bound of the confidence interval is above -10%, non-inferiority will be claimed.

A 95.3% unadjusted confidence interval will be used at 12 months. If the lower limit of the confidence interval (Q4W-Q2W) is above -10%, it is considered that the Arm 2 (6 mg/kg Q4W) is non-inferior to Arm 1 (3 mg/kg Q2W).

The OS and OS rates at 6 months and 12 months will be analyzed using the same method as for PFS and PFS rates.

Safety analysis: Safety will be analyzed through the incidence of deaths, AEs, serious adverse events (SAEs), AEs leading to discontinuation, AEs leading to dose interruption, select AEs and specific laboratory abnormalities (worst grade) in each arm. Toxicities will be graded using the NCI CTCAE version 4.0.

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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 (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS 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 BMS 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 (as per country guidelines) 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:

- 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.
- Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
- 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.
- 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.

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 his or her informed consent during the study, consent must additionally be obtained from the subject.

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 or subjects with or 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 his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing 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

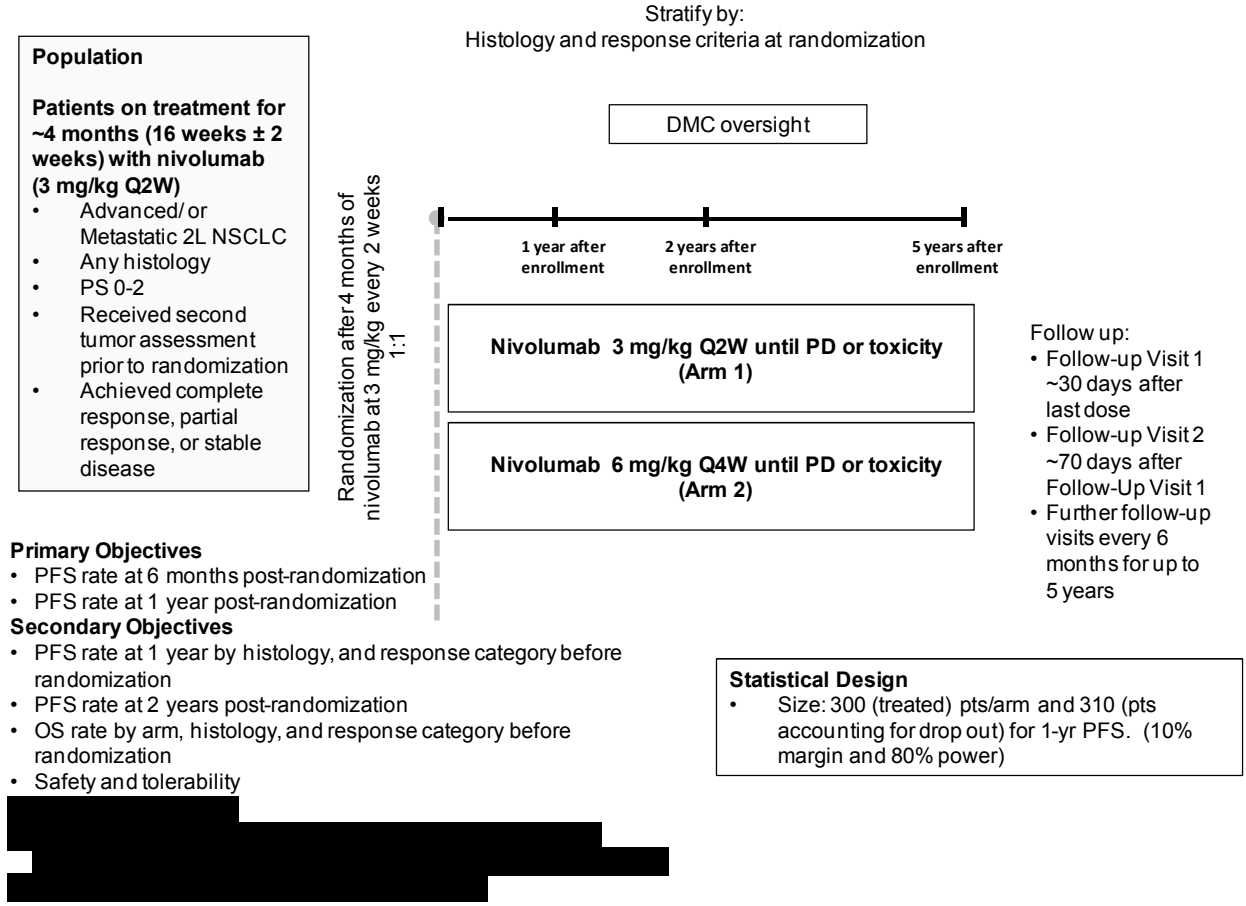
3.1 Study Design and Duration

Subjects will have received approximately 4 months (16 weeks ± 2 weeks) of nivolumab therapy at 3 mg/kg every 2 weeks and achieved a CR, PR, or SD as evidenced by a second tumor assessment prior to enrollment. At enrollment, subjects will be randomized 1:1 to receive either 3 mg/kg every 2 weeks (Arm 1) or 6 mg/kg every 4 weeks (Arm 2). Randomization will be stratified by histology and response criteria to pre-study nivolumab at randomization (CR or PR vs SD). For subjects receiving nivolumab 3 mg/kg every 2 weeks, each 14-day dosing period will constitute a cycle. For subjects receiving nivolumab 6 mg/kg every 4 weeks, each 28-day dosing period will constitute a cycle.

Subjects will continue treatment until disease progression or unacceptable toxicity for a maximum of 5 years from first randomized dose. The follow-up period begins when the decision to permanently discontinue a subject from study therapy is made (no further treatment or retreatment with nivolumab is anticipated) and will continue as specified in Table 5.1-3.

The study design schematic is presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



Each subject's last study visit will be defined as the last on-treatment or follow-up visit that occurs prior to the date of 5 years after the initiation of randomized therapy. The study will be completed no later than 5 years after the last subject's first visit.

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 BMS-supplied 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 BMS. BMS reserves the right to terminate access to BMS-supplied 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) Subjects with histologically or cytologically documented Sq- or non-SqNSCLC 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 chemoradiotherapy for locally advanced disease).

b) Subjects must have received and tolerated nivolumab 3 mg/kg every 2 weeks for approximately 4 months (16 weeks ± 2 weeks). Subjects may continue to receive pre-study nivolumab treatment during screening assessments as noted in Table 5.1-2. Subjects who receive nivolumab flat dosing are ineligible for this study.

c) Subjects must have at least 2 tumor assessments after the start of nivolumab and must demonstrate CR, PR, or SD to the pre-study nivolumab treatment on the latest scan within 28 days prior to randomization.

d) Subjects must have had measurable disease by CT or MRI per RECIST 1.1 criteria at the time of starting first dose of pre-study nivolumab treatment.

e) Subjects must have experienced disease progression or recurrence during or after at least 1 systemic platinum-based therapy for advanced or metastatic disease prior to starting the first dose of pre-study nivolumab.

   i) Each line of therapy should have been preceded by disease progression. A switch of an agent within a regimen in order to manage toxicity does not define the start of a new line of therapy.

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

   iii) Subjects who received platinum-based 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.

   iv) Subjects with recurrent disease > 6 months after platinum-based adjuvant, neoadjuvant or definitive chemoradiation therapy given for locally advanced disease, who also subsequently progressed during or after a platinum-based regimen given to treat the recurrence, are eligible.

   v) Subjects with a known activating EGFR mutation or ALK translocation are eligible if they have received an EGFR or ALK TKI in addition to a platinum-based chemotherapy

vi) Experimental therapies when given as a separate regimen are considered as a separate line of therapy.

f) ECOG PS 0-2

g) Subjects with stable CNS metastases 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 $\leq$ 10 mg daily prednisone (or equivalent).

h) All baseline laboratory requirements will be assessed and should be obtained within 14 days (unless otherwise specified in Table 5.1-1) of first dose of randomized nivolumab. Screening laboratory values must meet the following criteria:

i) WBCs $\geq$ 2000/µL

ii) Neutrophils $\geq$ 1500/µL

iii) Platelets $\geq$ 100 x 10^3/µL

iv) Hemoglobin $\geq$ 9.0 g/dL

v) Serum creatinine of $\leq$ 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 $\leq$ 3X ULN

vii) ALT $\leq$ 3X ULN

viii) Total bilirubin $\leq$ 1.5X ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

i) Palliative radiotherapy must be completed at least 2 weeks prior to enrollment.

j) Subject Re-enrollment: This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized/has not been treated). If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Males and Females, ≥ 18 years of age.

b) Women of childbearing potential (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 study drug.

c) Women must not be breastfeeding.

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (125 days) plus 30 days (duration of ovulatory cycle) for a total of 155 days or 23 weeks post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of nivolumab (125 days) plus 90 days (duration of sperm turnover) for a total of 31 weeks post-treatment completion. In addition, male subjects must be willing to refrain from sperm donation during this time.

f) Azoospermic males are exempt from contraceptive requirements. WOCBP who are continuously not heterosexually active are also exempt from contraceptive requirements, and still must undergo pregnancy testing as described in this section.

Investigators shall counsel WOCBP, and male subjects who are sexually active with WOCBP, on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise on the use of highly effective methods of contraception, which have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to use 1 highly effective method of contraception as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. WOCBP and female partners of male subjects, who are WOCBP, are expected to use one of the highly effective methods of contraception listed below. Male subjects must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner. Contraception methods are as follows:

1. Progestogen only hormonal contraception associated with inhibition of ovulation.
2. Hormonal methods of contraception including oral contraceptive pills containing combined estrogen + progesterone, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena®
3. Nonhormonal IUDs, such as ParaGard®
4. Bilateral tubal occlusion
5. Vasectomised partner with documented azoospermia 90 days after procedure
   - Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
6. Intrauterine hormone-releasing system (IUS)
7. Complete abstinence
   - Complete abstinence is defined as the complete avoidance of heterosexual intercourse (refer to Glossary of Terms).
   - Complete abstinence is an acceptable form of contraception for all study drugs and must be used throughout the duration of the study treatment (plus 5 half-lives of the investigational drug plus 30 days).

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- Subjects who choose complete abstinence must continue to have pregnancy tests, as specified in Section 6.4.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.
- The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

UNACCEPTALE METHODS OF CONTRACEPTION

- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with carcinomatous meningitis.

b) Subjects with untreated, symptomatic CNS metastases are excluded.

2. Medical History and Concurrent Diseases

a) Subjects with interstitial lung disease (eg, sarcoidosis) that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity. Subjects with chronic obstructive pulmonary disease whose disease is controlled at study entry are allowed.

b) Subjects with an 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.

c) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of first randomized dose of study drug with the exception of the subjects allowed to enroll with treated or active central nervous system (CNS) metastases requiring steroids. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

d) Subjects who received prior therapy with an anti-CTLA-4, anti-PD-L1, or anti-PD-L2, anti-CT137 (or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, except pre-study nivolumab) or subject is expected to require any other form of systemic antineoplastic therapy while receiving nivolumab.

e) 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 the subject's ability to comply with the study requirements, substantially increase the risk to the subject, or impact the interpretability of study results.

f) Other active malignancy requiring concurrent intervention.

g) 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 with the exception of anti-estrogen/androgen therapy or bisphosphonates.

h) All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

i) 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.

j) Known history of testing positive for Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome (AIDS).

3. Physical and Laboratory Test Findings

a) Positive 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

5. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated. (Note: under certain specific circumstances a person who has been imprisoned may be included or permitted to continue as a subject. Strict conditions apply, and Bristol-Myers Squibb approval is required.)

b) 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 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

Woman of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Females 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. The duration of the washout period below are suggested guidelines, and the investigators should use their judgment in checking serum FSH levels.

- 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. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- 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
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Criteria described in Section 4.5.3

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In the event a normal healthy female subject becomes pregnant during a clinical trial, the study drug must be discontinued immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the Medical Monitor within 24 hours of awareness of the pregnancy. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

If study drug is discontinued prior to the subject's completion of the study, the reason for the discontinuation must be documented in the subject's medical records and entered on the appropriate case report form (CRF) page.

3.6 Post Study Drug Study Follow up

In this study, PFS is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug 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 drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. 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 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 cause of 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. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. 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 STUDY DRUG

Study drug includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- Study required premedication (if applicable)

Table 4-1: Study Drugs for CA209384

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	10 mL per vial/	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

4.1 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.

The investigational product in this study is nivolumab.

4.2 Non-investigational 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 non-investigational products.

Not applicable.

4.3 Storage 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 BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Study drug not supplied by BMS will be stored in accordance with the package insert.

Investigational product documentation (whether supplied by BMS or not) 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).

4.4 Method of Assigning Subject Identification

CA209384 is a randomized study. 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 web-based response system (IWRS). Specific instructions for enrollment and randomization procedures using IWRS will be provided to the investigational site in a separate document/ manual. Subjects meeting all eligibility criteria and randomized into the study will be assigned to 1 of the 2 treatment arms and stratified by the following factors: histology and response at randomization (CR or PR vs SD).

Required information for registration includes, but is not limited to, the following:

- Response at randomization (CR or PR vs SD)

- Subject received and tolerated nivolumab 3 mg/kg every 2 weeks for approximately 4 months (16 weeks ± 2 weeks)
- ECOG status 0-2
- Planned date of first dose

Additional information required for registration in the study will be available in a separate document.

IWRS code will be provided to the analytical laboratories and to the PK scientists to facilitate PK sample analysis.

4.5 Selection and Timing of Dose for Each Subject

Subjects will enroll after receiving approximately 4 months (16 weeks ± 2 weeks) of nivolumab therapy and after receiving a second tumor assessment with evidence of a CR, PR, or SD.

Subjects in Arm 1 will receive 3 mg/kg of nivolumab intravenously as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle every 2 weeks, until progression, unacceptable toxicity, withdrawal of consent, or the subject reaches a maximum of 5 years from the first on-study dose, or the study ends, whichever occurs first. In this arm, each 14-day dosing period will constitute a cycle.

Subjects in Arm 2 will received 6 mg/kg nivolumab as a 30-minute (± 5 minutes) IV infusion on Day 1 of each treatment cycle every 4 weeks until progression, unacceptable toxicity, withdrawal of consent, or the subject reaches a maximum of 5 years from the first on-study dose, whichever occurs first. In this arm, each 28-day dosing period will constitute a cycle).

Subjects in Arm 1 may be dosed no less than 12 days from the previous dose; subjects in Arm 2 may be dose no less than 26 days from the previous dose.

Dosing calculations should be based on the body weight assessed at baseline. It is not necessary to re-calculate subsequent doses if the subject weight is within 10% of the weight used to calculate the previous dose. All doses should be rounded to the nearest milligram.

No dose escalations or reductions of nivolumab are allowed. There are no premedications recommended for nivolumab until infusion reactions have been observed in the subject. Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.5.5.

Dose delay criteria, criteria to resume treatment, and dose discontinuation criteria can be found in Section 4.5.1, Section,4.5.2 and Section 4.5.3, respectively.

4.5.1 Dose Delay Criteria

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 drug-related AE, with the following exceptions:
  - Grade 2 drug-related skin AEs, fatigue or laboratory abnormalities - no treatment delay required.
- Any Grade 3 skin, drug-related AE

- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, AST, ALT, or total bilirubin or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia 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 Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Medical Monitor should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

4.5.2 Criteria to Resume Treatment

Subjects may resume treatment with 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 Grade 1 AST/ALT or total bilirubin who require dose interruption 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 value
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.3) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Medical Monitor

Dose interruption of nivolumab which results in treatment interruption of > 6 weeks require treatment discontinuation, with exceptions as noted in Section 4.5.3. There will be no dose reductions for nivolumab.

4.5.3 Dose Discontinuation Criteria

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 for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require 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 > 5-10 × ULN for > 2 weeks
  - AST or ALT > 10 × ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 × ULN and total bilirubin > 2 × 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 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
  - 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
  - Grade 4 drug-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the Medical Monitor.
- Any event that leads to interruption in dosing lasting > 6 weeks from the previous dose requires discontinuation, 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 interruptions lasting > 6 weeks from the previous dose, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interruptions.

  - Dosing interruptions lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.5.4 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent 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
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab IB.

4.5.5 Treatment of Nivolumab-Related Infusion Reactions

Since 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, arthralgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grades 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 nivolumab administrations.

For **Grade 2** symptoms: (moderate reaction required 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 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 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 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 nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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).

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 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 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 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.

4.9 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 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.

4.10 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 Procedural Outline (CA209384)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	
Medical History	X	
Safety Assessments		
Physical Examination	X	Within 28 days prior to first randomized dose[a]
Vital Signs	X	Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable). Obtain vital signs at screening visit and within 72 hours of first randomized dose.
ECOG Performance Status	X	Within 28 days prior to first randomized dose[a]
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.
Serious Adverse Events Assessment	X	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.
Adverse Events Assessment	X	
Laboratory Tests: hematology, chemistry, liver function tests, thyroid function tests, Hepatitis B and C markers	X	EGFR mutations status should be documented if available. Labs performed locally within 14 days prior to randomization: Hematology includes WBC with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Chemistry includes BUN or urea level, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, glucose, lipase, amylase, and LDH. Liver function test includes aspartate aminotransferase (AST), alanine

Table 5.1-1: Screening Procedural Outline (CA209384)

Procedure	Screening Visit	Notes
		aminotransferase (ALT), total bilirubin, alkaline phosphatase (ALP), and albumin. Thyroid function test includes TSH. Reflexive free T3 and free T4 should be performed if TSH is abnormal. Results should be available prior to dosing. Hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCV Ab) should also be collected.
Review of Concomitant Medications	X	Within 14 days prior to first randomized dose[a]
Pregnancy Test (WOCBP only)	X	Serum or urine pregnancy test to be performed locally within 72 hours prior to first randomized dose.
Efficacy Assessments		
Tumor Assessments	X	Must be done within 28 days of first on-study dose. MRI of brain (with contrast, unless contraindicated) is required in subjects with a known history of treated brain metastases. [a] Additional sites of known or suspected disease (including CNS) should be imaged at the screening visit.
Outcome Assessments		
[redacted]	X	
Study Drug		
Randomize	X	

ANC, absolute neutrophil count; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BP, blood pressure; CNS, central nervous system; HR, heart rate; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; O2, oxygen; RR respiratory rate; WBC, white blood cell.

[a]Subjects may continue with the pre-study nivolumab treatment during the screening assessments.

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (±2 days)	Every 4 Weeks (±3 days)	Every 6 Weeks (±2 days)	Every 8 Weeks (±2 days)	Every 6 Months (±2 days)	End of Treatment	Notes
Safety Assessments							
Physical Examination	X						
Vital Signs	X					X	Within 72 hours prior to dosing and at EOT. Include temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest prior to dosing and at any time there are new or worsening respiratory symptoms.
[redacted]	X						Within 72 hours prior to each dose
Assessment of Signs and Symptoms	X						
Serious Adverse Event Assessment	X						Assessed using NCI CTCAE v. 4.0
Adverse Events Assessment	X						Assessed using NCI CTCAE v. 4.0
Laboratory Tests: hematology tests	X						Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count. Results should be available prior to dosing.
Laboratory Tests: chemistry tests	X						Chemistry (BUN or urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, and glucose), LDH. Results should be available prior to dosing.
Laboratory Tests: liver function test	X						Includes AST, ALT, total bilirubin, alkaline phosphatase, albumin. Completed within 72 hours of dosing. Results should be available prior to dosing.

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (±2 days)	Every 4 Weeks (±3 days)	Every 6 Weeks (±2 days)	Every 8 Weeks (±2 days)	Every 6 Months (±2 days)	End of Treatment	Notes
Laboratory Tests: thyroid function test			X[b]	X[c]		X	TSH should be evaluated every 3 cycles (6 weeks) in Arm 1 and every 2 cycles (8 weeks) in Arm 2 and EOT. However, reflexive free T3 and free T4 should be performed if TSH is abnormal. Results should be available prior to dosing.
Pregnancy Test (WOCBP only)		X					Serum or urine pregnancy test to be performed locally within 72 hours prior dosing.
Efficacy Assessments							
Tumor Assessments				X			Tumor assessment should be performed every 8 weeks (±1 week) for the first year of the study, then every 3 months for the second year of the study, followed by the local standard of care afterwards. Recommended to include chest, abdomen, pelvis, and all known sites of disease. Use same imaging method as was used at screening/baseline. Subjects with a history of brain metastasis should have surveillance MRI approximately every 12 weeks, or sooner if clinically indicated.
Survival Status	X						

Table 5.1-2: On-Treatment Assessments (CA209384)

Procedure[a]	Every Cycle (±2 days)	Every 4 Weeks (±3 days)	Every 6 Weeks (±2 days)	Every 8 Weeks (±2 days)	Every 6 Months (±2 days)	End of Treatment	Notes
Outcomes Research Assessment							
[redacted]					X		Should be completed prior to dosing.
[redacted]							
[redacted]		[redacted]					
[redacted]							
[redacted]	X						

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, Blood pressure; BUN, blood urea nitrogen; CTCAE, Common Terminology Criteria for Adverse Events; EOT, end of treatment; HR, heart rate, LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NCI, National Cancer Institute; [redacted]; O2, oxygen; RR, respiratory rate; TSH, thyroid stimulating hormone; WBC, white blood cell; WOCBP, women of childbearing potential.

[a] Assessments should start at Cycle 1 unless otherwise noted.

[b] Thyroid function tests should be performed every 6 weeks (every 3 cycles) for subjects in Arm 1 only.

[c] Thyroid function tests should be performed every 8 weeks (every 2 cycles) for subjects in Arm 2 only.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ±5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (±5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (±5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 5 years	Notes
Safety Assessments			
Physical Examination	X		
Vital Signs	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry (also monitor amount of supplemental oxygen if applicable)
[redacted]	X		
Assessment of Signs and Symptoms	X		
Serious Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4.0
Adverse Events Assessment	X		Assessed using NCI CTCAE v. 4.0
Laboratory Tests: hematology tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Includes WBC count with differential, ANC, lymphocyte count, hemoglobin, hematocrit, and platelet count.
Laboratory Tests: chemistry tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Chemistry (BUN or urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, bicarbonate, and glucose), LDH.

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ±5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (±5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (±5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 5 years	Notes
Laboratory Tests: liver function tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Includes AST, ALT, total bilirubin, ALP, albumin.
Laboratory Tests: thyroid function tests	X		Should be done at Follow-Up Visit 2 if results were abnormal at Follow-Up Visit 1. Reflexive free T3 and free T4 should be performed if TSH is abnormal.
Pregnancy Test (WOCBP only)	X		Serum or urine pregnancy test to be performed locally.
Efficacy Assessments			
Tumor Scans	See notes		For subjects without documented progression per RECIST 1.1, tumor scans should be completed as required by local standards of care or at the investigator's discretion
Subject Survival Status	X	X	Phone call or e-mail are acceptable if a clinical visit is not otherwise needed. Ad hoc data collection may be performed as needed.
Outcomes Assessments			

Table 5.1-3: Off-Treatment Follow-Up Assessments (CA209384)

Procedure	Follow-up Visits 1 (XO1) and 2 (XO2) XO1 to occur approximately 30 days ±5 days after last dose or coinciding with the date of discontinuation if the date of discontinuation (±5 days) is greater than 35 days after the last dose. XO2 to occur approximately 70 days after XO1 (±5 days)	Further Follow-Up Every 6 months (±1 month) after Follow-Up Visit 2 for up to 5 years	Notes
[redacted]	[redacted]	[redacted]	[redacted]

ALT, alanine aminotransferase; ALP, alkaline phosphatase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BP, blood pressure; CTCAE, Common Terminology Criteria for Adverse Events; HR, heart rate; RR respiratory rate; NCI, National Cancer Institute; O2, oxygen; TSH, thyroid stimulating hormone; WBC, white blood count; WOCBP, women of childbearing potential.

5.1.1 Retesting During Screening or Lead-in Period

Retesting of laboratory parameters and/or other assessments within any single Screening or Lead-in period will be permitted (in addition to any parameters that require a confirmatory value).

Any new result will override the previous result (ie, the most current result prior to Randomization) and is the value by which study inclusion will be assessed, as it represents the subject's most current, clinical state.

Laboratory parameters and/or assessments that are included in Table 5.1-1, Screening Procedural Outline may be repeated in an effort to find all possible well-qualified subjects. Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant.

5.2 Study Materials

The site will provide:

- All required materials for the tests performed locally (ie, relevant to clinical laboratory tests)
- A well-calibrated scale for recording body weight
- A calibrated sphygmomanometer
- Thermometer for temperature
- A validated temperature-controlled refrigerator
- [redacted]

BMS will provide:

- A BMS-approved protocol and any amendments or administrative letters (if required)
- Case report forms (electronic or hard copy)
- Nivolumab
- BMS-936558 (nivolumab) IB
- IWRS manual
- [redacted]
- Site manual including
  - RECIST 1.1 pocket guide
  - NCI CTCAE V4.0

5.3 Safety Assessments

Safety assessments will be conducted throughout the trial and during 100 days after the last dose of study treatment as described in Table 5.1-2 and Table 5.1-3. The assessments described in Table 5.1-2 should be monitored starting on Cycle 1 Day 1 (unless otherwise noted in the table) until discontinuation from study therapy.

Only data for the procedures and assessments specified in this protocol should be submitted to BMS on a case report form. Additional procedures and assessments may be performed as part of standard of care; however, data for these assessments should remain in the patient's medical record and should not be provided to BMS unless specifically requested. NCI CTCAE version 4.0 will be the criteria used to assess severity of AEs.

5.3.1 Imaging Assessment for the Study

Any incidental findings of potential clinical relevance that are not directly associated with the objectives of the protocol should be evaluated and handled by the Study Investigator as per standard medical/clinical judgment.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with Table 5.1-2 and should be performed, starting with Cycle 1 Day 1, according to RECIST 1.1 criteria.

High resolution CT with oral or 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 an alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments, including chest, abdomen, pelvis, brain, and all known or suspected sites of disease, should be performed within 28 days of first dose of study drug. Brain MRI is the preferred imaging method when evaluating CNS metastasis is necessary. In addition to chest and abdomen, all known or suspected sites of disease (including CNS) should be assessed 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 is 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 the target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response.

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 should be assessed by the investigator using RECIST 1.1.

[redacted]

[redacted]

6 ADVERSE EVENTS

An ***Adverse Event (AE)*** is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation subject administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease

temporally associated with the use of study drug, whether or not considered related to the study drug.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The causal 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.)

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320.

6.1 Serious Adverse Events

A S***erious Adverse Event (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 inpatient 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, pathogenic or nonpathogenic) 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).

Any component of a study endpoint that is considered related to study therapy (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported) should be reported as SAE (see Section 6.1.1 for reporting details).

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 other than to remedy ill health and 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).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited 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.

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

An SAE report must be completed for any event where doubt exists regarding its 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 must 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 of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy

surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must 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, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must 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 and for those 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 Result Abnormalities

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page or SAE Report Form electronic) as appropriate. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE

- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

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

6.4 Pregnancy

If, following initiation of the study drug, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of study exposure, including during at least 5 half lives after product administration, the investigator must immediately notify the BMS Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to BMS Designee within 24 hours of awareness of the event and in accordance with SAE reporting procedures described in Section 6.1.1.

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety). Please call the BMS Medical Monitor within 24 hours of awareness of the pregnancy.

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 of awareness of the event 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 BMS. 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, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be utilized to provide general oversight and safety considerations for this study. The DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in this study. The DMC will be charged with assessing such actions in light of an acceptable risk/benefit profile for nivolumab therapy. The DMC will act in an advisory capacity to BMS and will monitor subject safety data for the study approximately every 6 months for the duration of the trial.

The DMC will be advisory to the clinical study leadership team. The clinical study leadership 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 to the study conduct are required.

Details of the DMC responsibilities and procedures will be specified in the DMC charter.

When required, adjudicated events will be submitted to the DMC and Health Authorities for review on a specified timeframe in accordance with the adjudication documentation.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The primary analyses evaluate the non-inferiority of post-randomization 6-month and 12-month milestone PFS rate of nivolumab 6 mg/kg Q4W vs the PFS rate of nivolumab 3 mg/kg Q2W in subjects with disease control (CR/PR/SD) after approximately 4 months (16 weeks ± 2 weeks) of nivolumab 3 mg/kg Q2W treatment. The non-inferiority margin of -10% was chosen for this study. Patients who achieved CR, PR, or SD will be randomized after 4 months (16 weeks ± 2 weeks) of nivolumab treatment. It is estimated that the 12-month milestone PFS rate post-randomization is 0.384 with 3 mg/kg Q2W and 6-month PFS rate post-randomization is 0.52.

The sample size was computed based on a cumulative hazard function which account for both progression and censoring distributions. Using cumulative hazard function and its relation with

survival function, it is estimated that approximately 600 patients, 300 in each arm, will provide 80% power for the lower bound of a 95.3% one-sided confidence interval above -10% at the 12-month milestone and the lower bound of a 99.1% confidence interval above -10% at 6 months if PFS rates of the 2 arms are assumed to be equal. The experiment-wise error rate is maintained at one-sided 5% level.

To account for those who are randomized but not receiving treatment, 310 per arm will be randomized. With a 15% screen failure rate, approximately 730 subjects will be screened to achieve approximately 620 randomized subjects.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who signed an informed consent form and were registered into the IWRS.
- All randomized subjects: all subjects who are randomized to 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks. This is the primary population for efficacy analyses. Subpopulation analyses will be conducted by tumor histology (Sq or non-Sq) and response at randomization (PR or CR vs SD).
- All treated subjects: all randomized subjects who received at least 1 dose of nivolumab. This is the primary population for safety analyses. Subpopulation analyses will be conducted by tumor histology and response at randomization for some safety variables.
- PK subjects: all treated subjects with available serum time-concentration data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The coprimary objectives of this trial will be assessed by PFS rate at 6 months after randomization and PFS rate at 1 year after randomization. PFS is defined as the time from the date of randomization to the date of first documented tumor progression determined by the investigator or death, whichever is earlier. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. PFS rate at 6 months is the rate from Kaplan-Meier estimate 6 months after randomization; PFS rate at 1 year is the rate from Kaplan-Meier estimate at 1 year after randomization.

8.3.2 Secondary Endpoint(s)

Secondary objectives will be assessed by:

- PFS rate at 1 year after randomization by tumor histology and by response criteria
- PFS rate at 2 years after randomization
- OS rate at 1 year and OS up to 5 years by arm, histology, and response status at randomization. OS is defined as time from the date of randomization to the date of death. Subjects who did not die by the end of the study will be censored at the last known date alive. OS rate at 1 year is the rate from Kaplan-Meier estimated at one year after randomization.
- Safety and tolerability of nivolumab, as measured by incidence and severity of AEs and specific laboratory abnormalities

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographics and baseline disease characteristics including age, sex, race, ethnicity, weight, baseline disease diagnosis, and medical condition will be summarized using descriptive statistics by dose regimen.

8.4.2 Efficacy Analyses

PFS will be summarized by KM product-limit method and confidence interval for hazard ratio will be produced from a stratified (by tumor histology and response category) proportional hazard model. Median values of PFS, along with one-sided 95% CI using Brookmeyer and Crowley method, will be calculated. The status of subjects who are censored in the PFS Kaplan-Meier analysis will be tabulated for each dose regimen.

The 95% one-sided confidence intervals for PFS rates at 6 months and 12 months will be calculated for each dose regimen and difference between dose regimens using the Greenwood formula.

For the 6-month analysis, the 99.1% one-sided confidence interval around the difference in PFS rates between Q2W dose regimen and the Q4W regimen will be generated. If the lower bound of the confidence interval is above -10%, non-inferiority will be claimed.

A 95.3% unadjusted confidence interval will be used at 12 months. If the lower limit of the confidence interval (Q4W-Q2W) is above -10%, it is considered that the Arm 2 (Q4W) is non-inferior to Arm 1 (Q2W).

OS and OS rates at 6 months and 12 months will be analyzed using the same method as for PFS and PFS rates.

8.4.3 Safety Analyses

Safety will be analyzed through the incidence of deaths, AEs, SAEs, AEs leading to discontinuation, AEs leading to dose interruption, select AEs, and specific laboratory abnormalities (worst grade) in each arm. Toxicities will be graded using the NCI CTCAE version 4.0.

[redacted]

[redacted]

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

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
- BMS
- 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 done via an administrative letter, investigators must inform their IRB(s)/IEC(s).

9.1.2 Monitoring

BMS representatives will review data centrally to identify potential issues to determine a schedule of on-site visits for targeted review of study records.

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.

9.1.2.1 Source Documentation

The Investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original and attributable, whether the data are hand-written on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records (EMRs/EHRs), adverse event tracking/reporting, protocol required assessments, and/or drug accountability records).

When paper records from such systems are used in place of electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

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 BMS, 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 study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): N/A. 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 identification 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
- nonstudy 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 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 that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

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 electronic SAE form and Pregnancy Surveillance form, respectively. If electronic SAE form is not available, a paper SAE form can be used. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by BMS.

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, SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a 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 BMS. 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 as appropriate based on the following criteria:

- Study Steering Committee chair or their designee

The data collected during this study are confidential and proprietary to BMS. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement (CTA) governing [Study site or Investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to BMS at the earliest practicable time prior to submission or presentation and otherwise within the time period set forth in the CTA.

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Women must continue to have pregnancy tests. Acceptable alternate methods of highly or less effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALK	Anaplastic lymphoma kinase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CNS	Central nervous system
CRF	Case Report Form, paper or electronic
CR	Complete response
CrCl	Creatinine clearance
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EGFR	Epidermal growth factor receptors
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
IB	Investigator Brochure

Term	Definition
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IO	Immuno-oncology
IP	Investigational Product
IRB	Institutional Review Board
IV	intravenous
IWRS	Interactive web-based response system
kg	kilogram
Km	Kaplan-Meier
L	liter
LFT	Liver function test
mg	milligram
mL	milliliter
mmHg	millimeters of mercury
N	number of subjects or observations
N/A	not applicable
NCI	National Cancer Institute
NIMP	non-investigational medicinal products
Non-Sq	Non-squamous
NSCLC	Non-small cell lung cancer
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors

Term	Definition
RBC	red blood cell
SAE	serious adverse event
SD	Stable disease
SQ	Squamous
TKI	Tyrosine kinase inhibitors
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
VAS	Visual analog scale
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential