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Clinical Protocol CA209511

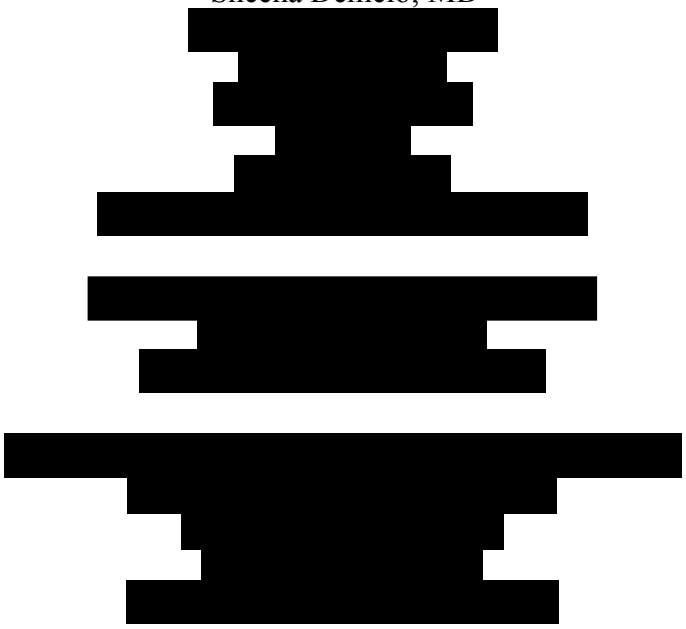
Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

(CheckMate 511: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 511)

Revised Protocol Number: 04

Study Director/Medical Monitor

Sheena Demelo, MD



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

SYNOPSIS

Clinical Protocol CA209511

Protocol Title: Phase IIIb/IV, Randomized, Double Blinded, Study of Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg vs Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):

- Arm A: nivolumab 3 mg/kg IV combined with ipilimumab 1 mg/kg (N3I1) IV every 3 weeks for 4 doses then flat dose nivolumab 480 mg every 4 weeks
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg (N1I3) IV every 3 weeks for 4 doses then flat dose nivolumab 480 mg every 4 weeks.

Study Phase: IIIb/IV

Research Hypothesis: Treatment with N3I1 will show a reduced rate of drug-related Grade 3 - 5 adverse events compared with N1I3 and have similar efficacy in patients with previously untreated, unresectable or metastatic melanoma.

Objectives:

- The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg to nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naive subjects with unresectable or metastatic melanoma.

Key secondary objectives include:

- To evaluate the objective response rate (ORR), as determined by investigators, of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg and nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naive subjects with unresectable or metastatic melanoma.
- To evaluate progression free survival (PFS) of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg and nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg in treatment-naive subjects with unresectable or metastatic melanoma.
- To assess overall survival (OS)
- To assess Health Related Quality of Life (HRQoL) using the European Organisation for Research and Treatment of Cancer (EORTC QLQ-C30).

[redacted]

Study Design:

This is a Phase IIIb/IV, randomized, double blinded, study of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg ipilimumab in combination with 3 mg/kg in adult subjects with previously untreated, unresectable or metastatic melanoma.

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

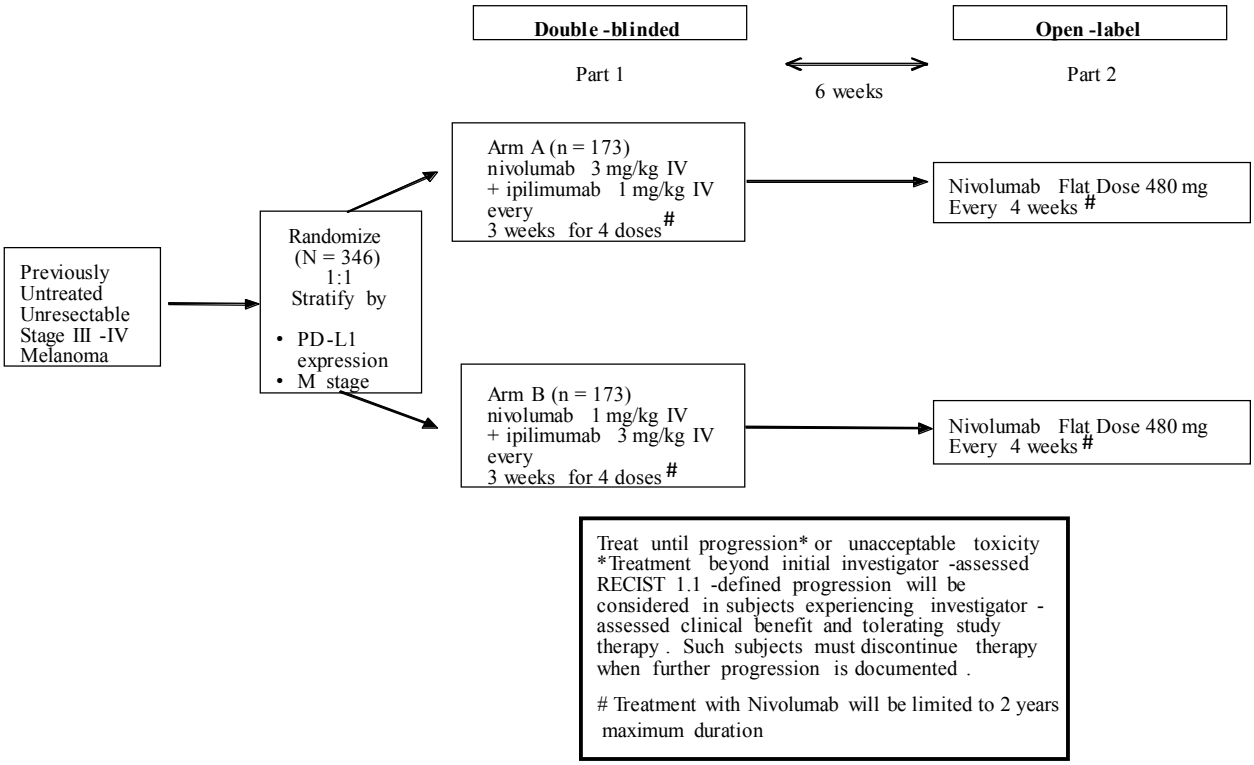
Subjects will be randomized 1:1 and stratified by programmed cell death receptor-ligand 1 (PD-L1) expression (≥ 5% tumor cell surface expression vs < 5% tumor cell surface expression/indeterminate), and American Joint Commission on Cancer (AJCC) M stage (M0/M1a/M1b vs M1c). Record of BRAF V600 status (mutant vs wildtype) must be provided (by local institutional standard), but not used for stratification.

On-treatment phase consists of Parts 1 and 2:

During Part 1, subjects will be treated every 3 weeks with the combination of nivolumab and ipilimumab for 4 cycles. A cycle will be defined as 3 weeks during Part 1.

During Part 2, subjects will be treated by nivolumab, flat dose 480 mg every four weeks, beginning 6 weeks after the last combination dose. A cycle will be defined as 4 weeks during Part 2.

Treatment will continue until progression or unacceptable toxicity in both arms, up to a maximum of 2 years treatment



Study Population:

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

- Adult subjects (≥ 18 years) with histologically confirmed unresectable Stage III or Stage IV Melanoma as per AJCC staging system.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1
- No prior systemic anticancer therapy for unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to date of first dose, and all related adverse events have either returned to baseline or stabilized.
- Measurable disease as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST) criteria
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the

screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.

- Known BRAF V600 mutation status as determined by local institutional standard or subject to consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible.

Key Exclusion Criteria:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no evidence of progression via magnetic resonance imaging (MRI, except where contraindicated in which CT scan is acceptable) for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Ocular melanoma
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

Subjects must also meet the study criteria including exclusion for medical history, positive hepatitis B/C, HIV and pregnancy tests, and the laboratory criteria described in Section 3.3.

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

Study Drug for CA209511		
Medication	**Potency**	**IP**
Nivolumab BMS-936558-01 Solution for Injection	100 mg (10 mg/mL)	10 mL per vial
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial

Study Assessments:

Adverse events will be collected to determine the incidence of drug-related adverse events between the two cohorts.

Subjects will be observed for tumor response (ORR and PFS).

Subjects will be assessed by computed tomography (CT) or magnetic resonance imaging (MRI) beginning Week 12 (± 1 week) from randomization and continuing every 8 weeks (± 1 week) for the first 12 months and then every 12 weeks (± 2 weeks) until disease progression.

Subjects will be followed for Overall survival (OS) after disease progression or after drug-discontinuation.

Patient reported outcomes will be collected using the EQ-5D and EORTC QLQ-30

Statistical Considerations:

Sample Size: Approximately 346 subjects will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 340 treated subjects (170 per arm). Given a two-sided alpha of 0.05, this number of treated subjects provides 80%

power to show a statistically significant difference in the rate of drug-related Grade 3 - 5 AEs between the two treatment arms, assuming a rate of 40% in Arm A and a rate of 55% in Arm B.

Endpoints: The primary endpoint is the incidence of drug-related Grade 3 - 5 AEs.

The secondary endpoints of the study are investigator determined ORR, PFS, OS, and HRQoL.

Analyses: For the primary analysis, we will report the drug-related Grade 3 - 5 AE rate by treatment arm, the difference in rates between arms, and the corresponding 95% confidence intervals. Two-sided CMH test, stratified by PD-L1 expression and M stage at screening, will be performed to compare the rate of drug-related Grade 3 - 5 AE rate between the two treatment arms.

ORRs and corresponding 95% exact Confidence Interval (CI)s will be calculated using the Clopper Pearson method for each of the treatment arms. BOR will be tabulated for each treatment group. The 2 treatment arms will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by PD-L1 expression and M stage at screening. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated, and a p-value will be presented for descriptive purposes. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology.

PFS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Median PFS and corresponding two-sided, 95% confidence intervals will be computed. Descriptive Hazard Ratio and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate stratified by PD-L1 expression and M Stage at screening. PFS rates at 6 months with 95% CIs will be estimated using KM methodology.

OS will be summarized descriptively using Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will be calculated. EORTC QLQ-C30 scale data will be summarized by timepoint using descriptive statistics for each treatment group.

TABLE OF CONTENTS

1.2 Research Hypothesis

Treatment with nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg (N3I1)-Arm A will show a reduced incidence of drug-related Grade 3 - 5 adverse events compared with nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg (N1I3)-Arm B and have similar efficacy in patients with previously untreated, unresectable, or metastatic melanoma.

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective is to compare the incidence of drug-related Grade 3 - 5 AEs of N3I1 to N1I3 in subjects with previously untreated, unresectable or metastatic melanoma.

1.3.2 Secondary Objectives

- To evaluate the ORR, as determined by investigators, of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To evaluate PFS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To assess OS of N3I1 and N1I3 in subjects with untreated, unresectable or metastatic melanoma.
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organization for Research and Treatment of Cancer (EORTC) QLQ-30.

[redacted]

1.4 Product Development Background

[redacted] by therapeutic vaccination or by modulating regulatory checkpoints of the immune system.

[redacted]

[redacted] rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02).[22]

[redacted]

[redacted]

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 Bristol Myers Squibb (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 informed consent form (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.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

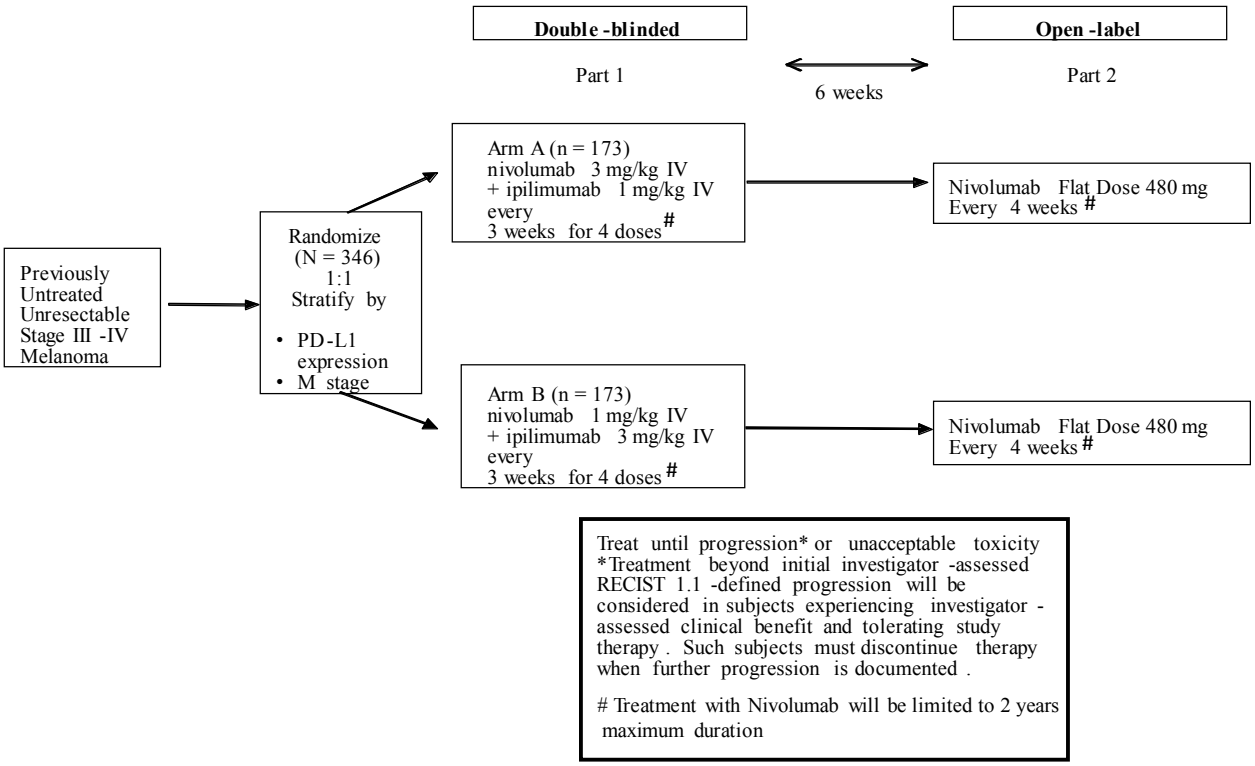
This is a Phase IIIb/IV, randomized, double blind, 2-arm study of nivolumab 3 mg/kg combined with ipilimumab 1 mg/kg vs nivolumab 1 mg/kg combined with ipilimumab 3 mg/kg, in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or metastatic Stage III or stage IV melanoma, as per the AJCC staging system, and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma.

Subjects will be randomized 1:1 and stratified by PD-L1 status and AJCC M stage as described below:

- PD-L1 expression level
  - PD-L1 ≥ 5% tumor cell surface expression (in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 < 5% tumor cell surface expression (in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- AJCC M stage at screening (See Appendix 4)
  - M0/M1a/M1b vs
  - M1c

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

Figure 3.1-1: Study Design Schematic



It is expected that 460 subjects will need to be enrolled in order to randomize 346, assuming a screen failure rate of 25%.

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

3.1.1 Screening Phase

- Begins by establishing the subject's initial eligibility and signing of the ICF.
- Subject is enrolled using the IRT
- Tumor tissue obtained in the metastatic setting or from an unresectable site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to the acquisition of additional tumor tissue for performance of biomarker analyses.

3.1.2 Treatment Phase

- Begins with the randomization call to the IRT.
- Subject will be randomized to:
  - Arm A (N3I1): nivolumab 3 mg/kg + ipilimumab 1 mg/kg administered every 3 weeks for 4 doses or
  - Arm B (N1I3): nivolumab 1 mg/kg + ipilimumab 3 mg/kg ipilimumab are administered every 3 weeks for 4 doses.
- After combination therapy, all subjects will receive a flat dose 480 mg nivolumab IV every 4 weeks, beginning 6 weeks after the last combination dose, until progression or unacceptable toxicity.
- Treatment with Nivolumab will be limited to 2 years maximum duration.
- A negative pregnancy test should be documented within 24 hours prior to start of each dose of investigational product.
- Within 3 days from randomization, the subject must receive the dose of study medication.
- On study laboratory assessments should be drawn within 72 hours prior to dosing
- PK samples and immunogenicity samples will be collected according to the schedule in Table 5.1-2 and Table 5.1-3
- Adverse event assessments should be documented at each clinic visit.
- Quality of Life will be assessed using European Organisation for Research and Treatment of Cancer Quality Of Life Questionnaire-core 30 (EORTC QLQ-C30) and European Quality of Life-5 Dimensions (EQ-5D) questionnaires, to be completed after randomization, prior to the first dose of study therapy and every 6 weeks for the first 6 months, and every 4 weeks until approximately week 40, according to the schedule in Table 5.1-2.
- Study drug dose may be delayed for toxicity. See Section 4.4.1.
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 12 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) for the first 12 months, and then every 12 weeks (± 2 week) until disease progression or treatment discontinuation, whichever occurs later.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5.

3.1.3 Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy). Patients will be followed for efficacy and OS.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 12 weeks (± 1 week) after randomization and continuing every 8 weeks (± 1 week) for the first 12 months from randomization, and every 12 weeks (± 2 weeks) thereafter until documented tumor progression.

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window as detailed in the Time and Events Table 5.1-4 Follow-up Assessments (CA209511). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

The total duration of the study from start of randomization to primary analysis of the study is expected to be approximately 13 months (7 months of accrual + 6 months of follow-up after last subject has been dosed), assuming an accrual rate of 58 subjects per month. Additional survival follow-up may continue for up to 5 years from the primary analysis. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug up to the maximum treatment duration of 2 years. 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 including the completion of quality of life questionnaires and other requirements of the study.

2. Target Population

a) Histologically confirmed melanoma (per AJCC staging system) that is unresectable or metastatic (Refer to Appendix 4)

b) ECOG Performance Status ≤ 1 (Refer to Appendix 2)

c) Treatment naïve subjects (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized.

d) Measurable disease by CT or MRI per RECIST 1.1 criteria Section 5.4.2.1.

e) Archival or recently acquired tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses."

f) Subjects with known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period, the results of which must be reported within 3 months of randomization. All BRAF statuses (BRAF wild-type or BRAF 600 mutation positive) are eligible.

g) Prior radiotherapy must have been completed at least 2 weeks prior to study drug administration.

h) Screening laboratory values must meet the following criteria (using CTCAE v4):

i) WBC ≥ 2000/uL

ii) Neutrophils ≥ 1500/uL

iii) Platelets ≥ $100x10^3$/uL

iv) Hemoglobin ≥ 9.0 g/dL

v) Serum creatinine ≤ 1.5 x upper limit of normal (ULN) or calculated creatinine clearance > 40 mL/min (using the 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 ≤ 3.0 x ULN

vii) ALT ≤ 3.0 x ULN

viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level of < 3.0x ULN).

3. Age and Reproductive Status

a) Males and Females, ages ≥ 18 years.

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) Women of childbearing potential (WOCBP) must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 30 days (duration of ovulatory cycle) plus the time required for the investigational drug to undergo approximately five half lives. WOCBP should therefore use an adequate method to avoid pregnancy for 5 months after the last dose of investigational drug (combination or monotherapy). Refer to Appendix 5.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception, as indicated in the informed consent form, for a period of 90 days plus the time required for the investigational drug to undergo approximately five half lives. Men who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for nivolumab to undergo approximately 5 half lives) after the last dose of investigational drug (combination or monotherapy). 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. (Refer to Appendix 5.)

The methods of contraception are also indicated in the informed consent form.

At a minimum, subjects must agree to the use one highly effective method of contraception.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI - except where contraindicated in which computed tomography (CT) scan is acceptable) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

b) Ocular melanoma.

2. Medical History and Concurrent Disease

a) Prior active malignancy within the previous 3 years except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancer, superficial bladder cancer, or carcinoma in situ of the prostate, cervix, or breast

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 randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

d) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD37, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways. This includes utilization of these agents in the adjuvant, neo-adjuvant, and metastatic melanoma setting.

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

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

g) Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.

3. Physical and Laboratory Test Findings

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

4. Allergies and Adverse Drug Reaction

a) History of allergy or hypersensitivity to study drug components

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

Women of childbearing potential (WOCBP) 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 judgement 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.

3.4 Concomitant Treatments

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted] alliative radiation therapy, or standard or investigational agents for treatment of cancer).

[redacted]

[redacted]

[redacted]

[redacted]

[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, 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 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
- Unblinding a subject for any reason (emergency or non-emergency)
- Pregnancy.

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 BMS 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).

Please also refer to Discontinuation Criteria in Section 4.4.4.

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, overall survival 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.

BMS may request that survival data be collected on all treated/randomized subjects outside of the protocol defined window (Table 5.1-1). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contacts or is lost to follow-up.

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:

Table 4-1: Study Drugs for CA209511

Product Description / Class and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection[a]	100 mg (10 mg/mL)	10 mL per vial	5 or 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
Ipilimumab	200 mg (5 mg/mL)	40 mL per vial/Open-label	4 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

[a] Nivolumab is labeled as BMS-936558-01 Solution for Injection.

Pre-medications or medications used to treat in infusion reactions should be sourced by the investigative sites if available and permitted by local regulations.

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.

In this protocol, investigational products are:

- Nivolumab
- Ipilimumab

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.

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).

4.3.1 Part 1 Study Drug Administration (Combination Portion)

In the nivolumab plus ipilimumab combination portion, nivolumab is to be administered first. Subjects should receive nivolumab at a dose of 3 mg/kg (Arm A) or 1 mg/kg (Arm B) as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the next infusion.

The second infusion in the combination cohort will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion and the infusion line has been flushed, filters changed and the patient has been observed to ensure no infusion reaction has occured.

Subjects should receive ipilimumab at a dose of 1 mg/kg (Arm A) or at a dose of 3 mg/kg (Arm B) as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks (within 3 calendar days of scheduled date) for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

The risk/benefit profile for nivolumab has primarily been investigated using a 60-minute infusion and for ipilimumab a 90-minute infusion. Long infusion times place a burden on patients and treatment centers. Establishing that these agents can be safely administered using shorter infusion times will diminish some of this burden. Previous clinical studies of nivolumab have used 60-minute infusion duration and for ipilimumab 90-minute. Both nivolumab and ipilimumab have been administered safely at doses ranging up to 10 mg/kg over these treatment durations. Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across multiple clinical studies, and all have been managed by following the safety algorithms. Infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared with the prior experience at 10 mg/kg nivolumab dose infused over the 60-minute duration. Similarly, shortened infusion duration of 30 minutes for ipilimumab is not expected to present additional safety concerns.[24]

Both agents given as single agent is uncommonly associated with infusion reactions, incidence less than 1% for ipilimumab (Yervoy® FDA Label) and for nivolumab 3%.[9] In the CA209069 study, hypersensitivity/infusion reactions were listed as 3.2% for the combination and 2.2% for ipilimumab. No Grade 3 or Grade 4 hypersensitivity/infusion reactions were observed in either the combination or single agent ipilimumab treatment groups.[25]

Subjects should be carefully monitored for infusion reactions during nivolumab/ipilimumab administration. If an acute infusion reaction is noted, subjects should be managed according to Section 4.4.

The **pharmacy manual** includes detailed instructions for study medication preparation.

Dosing calculations should be based on the body weight assessed at screening. 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.

During Part 1, subjects may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day.

Detailed instructions for dilution and infusion of nivolumab/ipilimumab injection may be provided in the pharmacy binder, pharmacy reference sheet or current investigator brochure.[23,26] Care must

be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

4.3.2 Part 2 Study Drug Administration (Maintenance)

Starting 6 weeks after the last co-administered dose in Part 1, subjects will be administered a flat dose 480 mg nivolumab IV as a 30-minute IV infusion every 4 weeks (Q4W) (± 3 days) until unacceptable toxicity or disease progression, up to a maximum of 2 years treatment.

Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Every effort should be made to adhere to protocol treatment schedule of administration of nivolumab every 4 weeks in the maintenance phase. In extenuating circumstances in which the patient cannot make the dosing schedule within the 3-day window, BMS Monitor should be contacted.

For details on prepared drug storage, preparation, and administration, please refer to the BMS-936558 (nivolumab) IB, the ipilimumab IB and/or pharmacy reference sheets.

4.4 Method of Assigning Subject Identification

CA209511 is a randomized, double-blind study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by accessing an Interactive Response Technologies web-based system (IRT) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IRT. Specific instructions for using IRT will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth
- Gender at birth.

Once enrolled in IRT, enrolled subjects that have met all eligibility criteria will be ready to be randomized through the IRT. The following information is required for subject randomization:

- Subject number
- Date of birth
- PD-L1 expression level (PD-L1 ≥ 5% expression vs PD-L1 < 5% expression/indeterminate) entered by vendor
- M Stage at screening (See Appendix 4).

Subjects meeting all eligibility criteria will randomize 1:1 ratio to Arm A (N3I1) or Arm B (N1I3) and stratified by the following factors:

- PD-L1 expression
- M stage.

The randomization procedures will be carried out via permuted blocks within each stratum. The exact procedures for using the IRT will be detailed in the IRT manual.

4.4.1 Dose Delay Criteria

Regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both, all study drugs must be delayed until treatment can resume (See Section 4.4.3). Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab and ipilimumab administration should be delayed for the following:

- Grade ≥ 2 non-skin, drug-related adverse event, with the exception of fatigue or laboratory abnormalities that do not require a treatment delay.
- Grade 2 drug-related creatinine, AST, ALT or Total Bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormality, with the following exceptions :
  - 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
  - Grade ≥3 AST, ALT, or total bilirubin will require discontinuation
  - 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.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

4.4.2 Dose Modifications

Dose reductions or dose escalations are not permitted. All dose modification rules apply to both Arms A and B given the blinded nature of this study.

4.4.3 Criteria to Resume Treatment

Subjects should resume treatment with nivolumab and ipilimumab in both arms A and B given the blinded nature of the study 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 Grade 2 AST/ALT or total bilirubin may resume treatment when laboratory values return to baseline and management with corticoids, if needed, is completed.
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.4.1) 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 BMS Medical Monitor.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the BMS Medical Monitor. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.4.1.

4.4.4 Discontinuation Criteria

All discontinuation criteria apply for nivolumab and ipilimumab in both Arms A and B (during Part 1) given the blinded nature of this study.

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 or recurs, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, diarrhea, hypersensitivity reactions, infusion reactions and endocrinopathies:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, 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. Adrenal insufficiency requires discontinuation, regardless of control with hormone replacement.
  - 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:
      - Grade ≥ 3 drug-related AST/ALT or Total Bilirubin abnormality
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- In most cases of Grade 3 AST or ALT elevation, study drugs) will be permanently discontinued. If the investigator determines a possible favorable risk/benefit ratio that warrants

continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Any Grade 4 drug-related adverse event or laboratory abnormality (including, but not limited to creatinine, AST, ALT, or total bilirubin), except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leucopenia
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis.
  - 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 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 BMS Medical Monitor.
- Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:
  - Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
  - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor.
- Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.
- 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.

4.4.5 Treatment Beyond Disease Progression

Accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of Progressive Disease (PD).

Subjects will be permitted to continue treatment beyond initial RECIST 1.1 defined PD, up to a maximum of 2 years treatment, as long as they meet the following criteria:

- Investigator-assessed clinical benefit, and
- Subject is tolerating study drug.
- Stable performance status

- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional study medication, All other elements of the main informed consent including the description of reasonably foreseeable risks or discomforts, or other alternative treatment options will still apply.

A radiographic assessment/scan should be performed within 6 weeks of initial investigator-assessed progression to determine whether there has been a decrease in the tumor size or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with nivolumab.

If the investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Time and Events Schedule on Section 5.

For the subjects who continue study therapy beyond progression, further progression is defined as an additional 10% increase in tumor burden with a minimum of 5 mm absolute increase from time of initial PD. This includes an increase in the sum of diameters of all target lesions and/ or the diameters of new measurable lesions compared to the time of initial PD. Treatment with study medication should be discontinued permanently upon documentation of further progression.

New lesions are considered measureable at the time of initial progression if the longest diameter is at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). Any new lesion considered non-measureable at the time of initial progression may become measureable and therefore included in the tumor burden if the longest diameter increases to at least 10 mm (except for pathological lymph nodes which must have a short axis of at least 15 mm). In situations where the relative increase in total tumor burden by 10% is solely due to inclusion of new lesions which become measurable, these new lesions must demonstrate an absolute increase of at least 5 mm.

4.4.6 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 and ipilimumab are considered I-O agents in this protocol. Early recognition and management of AEs associated with I-O 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 Appendix 3.

4.4.7 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab 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 Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

- Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms: (moderate reaction required therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, non-steroidal antiinflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for ≤ 24 hours):

- Stop the study drug 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 study medication 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 and/or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone 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 study drug. 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. Study drug 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).

4.5 Selection and Timing of Dose for Each Subject

The dosing regimen and schedule for Parts 1 and 2 are detailed in Table 4.5-1 and Table 4.5-2, respectively.

Note: The first flat dose 480 mg nivolumab in Part 2 will be administered 6 weeks after the last combination dose in Part 1.

Table 4.5-1: Dosing Schedule for Part 1 (Double-Blinded)

	Every 3 weeks dosing 1 cycle = 3 weeks			
	Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
Arm A	Nivolumab 3 mg/kg Ipilimumab 1 mg/kg	Nivolumab 3 mg/kg Ipilimumab 1 mg/kg	Nivolumab 3 mg/kg Ipilimumab 1 mg/kg	Nivolumab 3 mg/kg Ipilimumab 1 mg/kg
Arm B	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg	Nivolumab 1 mg/kg Ipilimumab 3 mg/kg

Table 4.5-2: Dosing Schedule for Part 2 (Open Label)

	Every 4 weeks dosing 1 cycle = 4 weeks, Cycle 5 to begin 6 weeks after Cycle 4[a]
	Cycle 5 and beyond
Arms A and B	Flat dose 480 mg nivolumab

[a] Cycle X - Cycle 8, 9, etc until disease progression or unacceptable toxicity or a maximum treatment of 2 years.

4.6 Blinding/Unblinding

The sponsor, subjects, investigator, and site staff will be blinded to the study drug administered during Part 1 (Combination Portion) of the study. Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation.

During Part 2 (monotherapy portion), 480 mg nivolumab administered as a flat dose will be open-label. However, subject's treatment assigned arm during Part 1 must not be revealed until end of study.

Blinding of treatment assignment is critical to the integrity of this clinical study. Hence, every effort should be made to maintain the blind. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, ie, that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not related to the investigational product, the problem may be properly managed by assuming that the subject is receiving active product. It is highly desirable that the decision to unblind treatment assignment be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind. The Principal Investigator should only call in for emergency unblinding AFTER the decision to discontinue the subject has been made.

- For this study, the method of unblinding for emergency purposes is through IRT. For information on how to unblind form emergency, please consult the IRT manual.
- In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.
- Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor.

Designated staff of Bristol-Myers Squibb Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples.

4.7 Treatment Compliance

Treatment compliance will be monitored by drug accountability as well as the subject's medical record and electronic case report form (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 Assessments (CA209511)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	Prior to any screening procedures.
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization.
Medical History	X	
Tumor Tissue Samples	X	Sufficient tumor tissue obtained in the metastatic setting or from an unresectable site (block or minimum of 10 slides, obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen) In order to be randomized, a subject must be have quantifiable PD-L1 expression (≥ 5% or < 5% tumor cell membrane staining) or be classified as PD-L1 indeterminate.
Safety Assessments		
Physical Examination	X	Including pulmonary assessment
Vital Signs	X	Including BP, HR, temperature. **Obtain vital signs at the screening visit and within 72 hours prior to first dose**. (Section 5.3)
Physical Measurements (including performance status)	X	Height, Weight and ECOG Performance status
Assessment of Signs and Symptoms	X	Within 14 days prior to first dose
Concomitant Medication Collection	X	Within 14 days prior to first dose
Laboratory Tests	X	CBC w/differential, Chemistry panel including: Albumin, LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, hepatitis B surface antigen (HBV sAg), and hepatitis C antibody (HCV Ab) or Hepatitis C RNA (HCV RNA), within 14 days prior to randomization

Table 5.1-1: Screening Assessments (CA209511)		
Procedure	**Screening Visit**	**Notes**
Pregnancy Test (WOCBP only)	X	
Screening/Baseline Tumor Assessment	X	Chest, Abdomen, Pelvis, and Brain within 28 days prior to first dose. Head MRI is required in subjects with known history of brain metastases; subjects without known history of brain metastases may have head CT or MRI.

Table 5.1-2: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)** **Cycle 1, 2, 3, 4 (Day 1)**	**Notes**
Safety Assessments		
Targeted Physical Examination	X	To be performed only as clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature. (Section 5.3)
Physical Measurements (including performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Within 72 hrs prior to dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (+ reflex Free T4 and Free T3), albumin if clinically indicated).
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to administration of first dose and every 3 weeks thereafter in Part 1 of the study.
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	See Section 5.5 for details regarding specific sample timing	
PK Samples	See Section 5.5 for details regarding specific sample timing	

Table 5.1-2: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)** **Cycle 1, 2, 3, 4 (Day 1)**	**Notes**
Exploratory Biomarker Testing		
Exploratory Serum Biomarkers	X	To be collected pre-dose; before first 4 combination doses only.
Peripheral Blood Mononuclear Cells (PBMCs)	X	To be collected pre-dose; before first 4 combination doses only. To be collected in USA and Canada only.
Whole Blood Sample (DNA)	X	X = before first combination dose only.
Myeloid-Derived Suppressor Cell (MDSCs)	X	To be collected pre-dose; before the first and the third combination dose only
Efficacy Assessment		
Tumor Assessment	See Notes	FIRST tumor assessment should be performed at 12 weeks (± 1 wk) following randomization. CT Chest, CT (or MRI) 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

Table 5.1-2: On-Study Assessments Part 1 (CA209511)		
Procedure	**For Part 1, Study Drug Every 3 Weeks for 4 Cycles (Both Arm A and Arm B)**	**Notes**
	Cycle 1, 2, 3, 4 (Day 1)	
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D	X	To be completed at the start of the clinic visit every 6 weeks. First questionnaire should be completed after IRT randomization but before dosing. (Cycle 1, 3)
Health Care Utilization	X	Health Care Utilization will be collected at each visit
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	Within 24 hours prior to dosing
Administer Study Treatment	X	First dose to be administered within 3 days following randomization. See Section 4.3.

Table 5.1-3: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4**
Safety Assessments		
Targeted Physical Examination	X	To be performed only if clinically indicated within 72 hours prior to dosing
Vital Signs	X	Including BP, HR, temperature (Section 5.3)
Physical Measurements (including performance status)	X	Weight and ECOG Performance status within 72 hours prior to dosing
Adverse Events Assessment	Continuously	
Review of Concomitant Medications	X	
Laboratory Tests	X	Beginning at Cycle 5 and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc), on-study local laboratory assessments should be done within 72 hours prior to the first (Part 2) dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. (Albumin if clinically indicated) Beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc), on-study local laboratory assessment should be done within 72 hours prior to the second (Part 2) dose and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.
Pregnancy Test (WOCBP only)	X	Serum or urine within 24 hours prior to first dose and every 4 weeks thereafter in Part 2

Table 5.1-3: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4**
Outcomes Research Assessments		
EORTC QLQ-C30 and EQ-5D	X	To be completed at the start of the clinic visit every 4 weeks from Cycles 5 to 11
Health Care Utilization		Health Care Utilization will be collected at each visit
Pharmacokinetic and Immunogenicity Assessments		
Immunogenicity blood sample	See Section 5.5 for details regarding specific sample timing	
PK Samples	See Section 5.5 for details regarding specific sample timing	
Efficacy Assessment		
Tumor Assessment	See Notes	First tumor assessment during Part 2 should occur after 8 weeks (± 1wk) relative to previous tumor assessment performed at week 12. Subsequent tumor assessments should occur every 8 weeks (± 1 wk) for the first 12 months from randomization. From the second year from randomization, tumor assessments should occur every 12 wks (± 2 wk) until disease progression. CT Chest, CT (or MRI) 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.

Table 5.1-3: On-Study Assessments - Part 2 (CA209511)		
Procedure	**For Part 2, Study Drug is Administered Every 4 Weeks (Both Arm A and Arm B)** **Cycle 5 and beyond (Day 1)**	**Notes** **Cycle 5 will begin 6 weeks after Cycle 4**
Clinical Drug Supplies		
IRT Drug Vial Assignment	X	
Administer Study Treatment	X	See Section 4.3. Note: Within 3 days from vial assignment, the subject must receive the dose of study medication.

Table 5.1-4: Follow-up Assessments (CA209511)			
Procedure	**Follow Up,[a] Visits X1 and X2**	**Survival,[b] Follow-up Y Visits**	**Notes**
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Event Assessments	X	X	
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN, creatinine, amylase, lipase and TSH (+ reflex Free T4 and Free T3) for X1, repeat at X2 if study drug related toxicity persists.
Pregnancy Test (WOCBP Only)	X		Serum or urine
Review of Concomitant Medications	X		
Pharmacokinetic Samples and Immunogenicity Assessments			
PK Samples	X		See Section 5.5 for schedule of assessments
Immunogenicity blood sample	X		Refer to Section 5.5 for details regarding specific sample timing
Survival Status			
Subject Status	X	X	Every 3 months, Survival Follow up Visits may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy

Table 5.1-4: Follow-up Assessments (CA209511)			
Procedure	**Follow Up,[a] Visits X1 and X2**	**Survival,[b] Follow-up Y Visits**	**Notes**
Efficacy Assessments			
Tumor Assessments	See Notes		Only for subjects without progression on study therapy. FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization SUBSEQUENT tumor assessments should occur every 8 weeks (± 1 wk) thereafter for the first 12 months, then every 12 wks (± 2 wk) until disease progression CT Chest, CT (or MRI) 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
Exploratory Biomarker Testing			
Tumor Tissue Biopsy	X	X	Optional; collection upon progression

[a] X visits occur as follows - X1 = 30 days from the last dose (± 7 days) or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose, X2 = 84 days (± 7 days) from follow-up visit 1. Follow up visits X1 and X2 will occur only after patient completes all study treatment.

[b] Y Survival visits = every 3 months from X2 (± 7 days).

5.1.1 Retesting During Screening

Any new result will override the previous result (i.e., 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.

5.2 Study Materials

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) IB
- Ipilimumab IB
- Pharmacy Information Sheets
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IRT, including enrollment worksheets
- Manual for entry of local laboratory data
- Serious Adverse Events (or eSAE) case report form pages
- Pregnancy surveillance forms
- RECIST 1.1 pocket guide
- Quality of Life questionnaires.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, blood pressure (BP), heart rate (HR) and temperature should be performed within 28 days prior to randomization. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period (see Table 5.1-1).

Baseline local laboratory assessments should be done within 14 days prior to the randomization and include: CBC with differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, albumin, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3, and Hep B and C testing (HBV sAg and HCV RNA or Ab) (see Table 5.1-1).

Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 3 weeks during Part 1, every 4 weeks during Part 2, and at the safety follow up visits (Follow up visits 1 and 2).

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase (Table 5.1-4), toxicity assessments should be done in person. Once subjects reach the survival follow-up phase, either in-person visits or documented telephone calls to assess the subject's status are acceptable.

Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0.

On-study weight, ECOG performance status, and vital signs should be assessed at each on-study visit prior to nivolumab dosing. Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. The start and stop time of the nivolumab infusion should be documented. Physical examinations are to be performed as clinically indicated (including a pulmonary assessment at screening). If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

During Part 1, on-study local laboratory assessments should be done within 72 hours prior to each dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3 and albumin if clinically indicated.

During Part 2, on-study local laboratory assessments should be done within 72 hours prior to the first (Part 2) dose beginning at Cycle 5 (Week 18) and every alternate dose thereafter (Cycle 7, 9, 11, 13, etc) and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3 and albumin if clinically indicated.

During Part 2, on-study local laboratory assessment should be done within 72 hours prior to the second (Part 2) dose (beginning at Cycle 6 and every alternate dose thereafter (Cycle 8, 10, 12, 14, etc) and include: LFTs (ALT, AST, total bilirubin, alkaline phosphatase) and creatinine.

Additional measures, including non-study required laboratory tests, should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Some of the previously assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5.1. Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 12 weeks (± 1 week) from randomization and continuing every 8 weeks (± 1 week) for the first 12 months and every 12 weeks (± 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

Radiographic images will be collected and sent to a centralized imaging core laboratory for storage and potential future central reading.

5.4.1 Primary Efficacy Assessment

Efficacy assessment is not a primary endpoint. The primary endpoint is the incidence of drug-related Grade 3 - 5 AEs. See Section 6 for a further description of adverse event reporting.

5.4.2 Secondary Efficacy Assessments

The secondary measure of efficacy will include the ORR and PFS.

The ORR, will be determined by the investigator using RECIST 1.1 criteria, in all treated subjects. ORR and is defined as the number of subjects with a BOR of complete response (CR) or partial response (PR) divided by the number of treated subjects. The investigator-determined ORR will be further characterized by the investigator-determined duration of response (DOR) and the magnitude of reduction in tumor volume

The other secondary efficacy measure will be to evaluate PFS in all treated patients.

Additional secondary endpoints include OS in all treated subjects.

Radiographic images will be collected and sent to a centralized imaging core laboratory for storage and potential future central reading.

5.4.2.1 Measurable Lesions

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

- 10 mm by CT/MRI scan (CT/MRI scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable)
- 20 mm by chest x-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow up, only the short axis will be measured and followed.

5.4.2.2 Non-measurable Lesions

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.

- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.4.2.3 Special Considerations Regarding Lesion Measurability

Bone Lesions

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

Cystic Lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are by definition, simple cysts.

"Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic lesions are present in the same subject, these are preferred for selection as target lesions.

Non-measurable Lesions

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

5.4.3 Specifications for Method of Measurement

5.4.3.1 Measurement of Lesions

All measurements should be recorded in metric notation (mm). All baseline evaluations should be performed as close as possible to the treatment start and never more than 28 days before the beginning of treatment.

5.4.3.2 Method of Assessment

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

5.4.3.3 CT/MRI Scan

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

5.4.3.4 Chest X-Ray

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

5.4.3.5 Clinical Lesions

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

5.4.3.6 Ultrasound

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

5.4.3.7 Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised.

5.4.3.8 Tumor Markers

Tumor markers such as, but not limited to, LDH may be used for clinical management, but will not be included in the assessment of BOR.

5.4.4 Baseline Documentation of "Target" and "Non-Target Lesions"

5.4.4.1 Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

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

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted below, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST 1.1 determined response.

5.4.4.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.4.3 Non-target Lesions

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

5.4.5 Tumor Evaluation

Evaluation of Target Lesions

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

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

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

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

5.4.5.1 Target Lesions that Become "Too Small to Measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). If the radiologist is able to provide an actual measurement, that should be recorded, even if it is below 5 mm.

5.4.5.2 Target Lesions that Split or Coalesce on Treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum.

As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they

are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

5.4.5.3 Evaluation of Non-target Lesions

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

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

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

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

5.4.5.4 Unequivocal Progression in Non-target Disease

To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.

A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status.

5.4.5.5 New Lesions

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

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

5.4.6 Response Criteria (RECIST 1.1)

For subjects who have measurable disease at baseline, Table 5.4.6-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.6-1: Time Point Response - Subjects with Target (± Non-target) Disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=Complete response, PR=Partial Response, SD=Stable Disease, PD=Progressive Disease, NE=Not evaluable

5.4.6.1 Missing Assessments and Not Evaluable Designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not have changed the assigned time-point response.

5.4.6.2 Confirmation of Scan

Verification of Response: As per RECIST 1.1, confirmation of response is required for trials with response as a primary endpoint but is no longer required in randomized studies since the control arm serves as appropriate means of interpretation of data. Hence, confirmation is NOT required.[27]

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered not to have progressive disease per RECIST 1.1.

5.4.6.3 Best Overall Response

The BOR is determined once all the data for the subject is known. It is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST1.1 or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. The subject's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

For the purpose of this study, the minimum scan time from baseline for determination of SD will be 12 weeks.

5.4.6.4 Duration of Objective Response

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

5.5 Pharmacokinetic and Immunogenicity Assessments

Samples for PK and immunogenicity assessments will be collected for all subjects receiving nivolumab and ipilimumab as described in Table 5.5.1-1. All timepoints are relative to the start of study drug administration. All on-treatment timepoints are intended to align with days on which study drug is administered. If it is known that a dose is going to be delayed, then the predose sample should be collected just prior to the delayed dose. However, if a predose sample is collected but the dose is subsequently delayed, an additional predose sample should not be collected. Further details of sample collection, processing, and shipment will be provided in the laboratory procedures manual.

Blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. All samples collected pre-dose should be taken just prior to the administration from the contralateral arm (ie, the arm not used for the infusion). If the infusion was interrupted, the interruption details will also be documented on the CRF. Blood samples will be processed to collect serum and stored preferably at -70°C (samples may be stored at -20°C up to 2 months). Further details of pharmacokinetic sample collection and processing will be provided to the site in the lab manual.

Blood samples for immunogenicity analyses of nivolumab and/or ipilimumab will be collected according to the schedule given in Table 5.5.1-1. Samples collected from subjects will be evaluated for the development of Anti-Drug Antibody (ADA) for nivolumab and/or ipilimumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab. Neutralizing ADA testing conditional upon assay availability.

5.5.1 Pharmacokinetic and Immunogenicity Sample Analyses

The serum samples will be analyzed for drug (nivolumab and ipilimumab) and ADA (anti-nivolumab and anti- ipilimumab antibodies) by validated immunoassays. Samples with a positive ADA response may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab.

In addition, selected serum samples may be analyzed by an exploratory method that measures nivolumab and ipilimumab, or detect anti-drug antibodies for technology exploration purposes; exploratory results will not be reported. The corresponding serum samples designated for either PK, immunogenicity or biomarker assessments may also be used for any of those analyses, if required (eg, insufficient sample volume to complete testing or to follow up on suspected immunogenicity related AE).

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sample Collections (CA209511)

Part[a]	Study Day[b] (1 Cycle = 3 weeks for Part 1 1 Cycle = 4 Weeks for Part 2)	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
1	C1D1	(Predose)[c]	00:00	X	X	X	X
1	C1D1	(EOI-nivo)[d]	00:90	X			
1	C1D1	(EOI-ipi)[d]	00:30			X	
1	C2D1	(Predose)[c]	00:00	X	X	X	X
1	C2D1	(EOI-nivo)[d]	00:90	X			
1	C2D1	(EOI-ipi)[d]	00:30			X	
1	C3D1	(Predose)[c]	00:00	X	X	X	X
1	C3D1	(EOI-nivo)[d]	00:90	X			
1	C3D1	(EOI-ipi)[d]	00:30			X	
2	C5D1	(Predose)[c]	00:00	X	X	X	X
2	C5D1	(EOI-nivo)[d]	00:30	X			
2	C9D1	(Predose)	00:00	X	X		

Table 5.5.1-1: Pharmacokinetic and Immunogenicity Sample Collections (CA209511)

Part[a]	Study Day[b] (1 Cycle = 3 weeks for Part 1 1 Cycle = 4 Weeks for Part 2)	Time (Event)	Time (Relative to Start of Nivolumab Infusion) Hours:Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenic Blood Sample for Ipilimumab
2	CXD1: Every 16 weeks after C09 (ie, C13D1, C17D1, etc.)	(Predose)	00:00	X	X		
	First 2 Follow-up Visits (Approximately up to 100 Days from the Discontinuation of Study Drug)	NA		X	X		

[a] Part 1 indicates first 12 weeks (or 4 cycles) of combination treatment (nivolumab + ipilimumab). Part 2 indicates nivolumab monotherapy period starting from Week 16 (or Cycle 5).

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

[c] Predose: All predose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab infusion.

[d] EOI-nivo and EOI-ipi: End of Infusion samples for nivolumab and ipilimumab, respectively. **For sequential dosing, both EOI samples should be collected immediately (preferably within 2 - 5 minutes) prior to the end of the ipilimumab infusion**. If the end of infusion is delayed, the collection of the EOI samples should be delayed accordingly. EIO samples may not be collected from the same IV access as drug was administered, refer to the laboratory manual for additional instructions.

[redacted]

5.6.1 Tumor Tissue Specimen

Pre-treatment tumor tissue specimens in the form of a paraffin embedded block or a minimum of 10 unstained slides will be submitted for central PD-L1 immunohistochemistry (IHC) assessment prior to randomization. These biopsy samples should be excisional, incisional, punch or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. PD-L1 stained tissue sections will be assessed by a pathologist and scored as PD-L1 expression ≥ 5% or PD-L1 expression < 5% based on the frequency of tumor cell surface PD-L1 staining among a minimum of a hundred (100) evaluable tumor cells. Where membrane staining is obscured by high cytoplasmic staining or melanin content, but the tumor tissue sample contain the minimum number of evaluable tumor cells, samples will be deemed PD-L1 indeterminate.

Tumor samples will be stained for PD-L1 by ICH and the stained tissue sections will be assessed by a pathologist for tumor and immune cell membrane expression of PD-L1. These tumor samples may also be assessed for the expression of other immune or melanoma related genes, RNAs and/or proteins, as well as, the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to IHC, qRT-PCR, genetic mutation detection, fluorescent in-situ hybridization (FISH) and exome sequencing. Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, ipilimumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed.

Tumor tissue samples may also be collected upon progression. This sample may be used for the assessment of markers implicated in resistance to immunotherapeutic agents, including but not limited to other T cell checkpoint receptors and ligands (eg, Lag-3, Tim-3) and intratumoral immune cell subsets, including but not limited to, T regulatory cells and myeloid derived suppressor cells. These samples may also be used to investigate the effect of nivolumab + ipilimumab on the expression of potentially relevant predictive and/or prognostic melanoma biomarkers, including, but not limited to PD-L1. Both the pre-treatment tumor sample

and the sample collected upon recurrence may be retrospectively assessed for BRAF mutation status, as well as for the expression of other immune or melanoma related genes.

[redacted]

5.6.3 Peripheral Blood Mononuclear Cells (PBMCs)

Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Section 5.1 for additional details on the blood sample collection schedule) for PBMC preparation, except at sites where the stability of the samples after shipment to the Central Laboratory cannot be guaranteed. Samples must be shipped within 48 hours to a BMS-designated central laboratory for processing.

These PBMC samples may be used for immunophenotyping or characterization of the immune cell subsets in the periphery, including, but not limited to, T cells, B cells, NK cells, or subpopulations of the aforementioned immune cell types. These samples may also be used to assess immune cell function or antigen specific T cell proliferation or activation pending emerging information from other nivolumab or ipilimumab studies.

5.6.4 Whole Blood for SNP Assessment

Whole blood samples for exploratory pharmacogenetic assessment will be collected from all subjects and put in frozen storage. Genomic DNA will be extracted and subsequently assessed for single nucleotide polymorphisms (SNPs) and other genetic variations in genes that may predispose subjects to nivolumab or ipilimumab benefit or adverse events (unless restricted by local requirements.) Such genes include, but are not limited to PD-1, PD-L1, PD-L2 and CTLA-4. Additional use of these data may include correlative analyses aimed at identifying genotypic associations with clinically-relevant biomarkers identified by other methodologies described in this section.

5.6.5 Myeloid-Derived Suppressor cells

Myeloid derived suppressor cells (MDSCs) are an immune cell population capable of suppressing T cell activation and proliferation. Low pre-treatment MDSC levels in peripheral blood may be associated with better overall survival in melanoma patients treated with the immunotherapeutic agent ipilimumab.[28] MDSCs will be measured at baseline and on-treatment to assess pharmacodynamic changes or associations with outcome (see Section 5.6.3 for additional details on the blood sample collection schedule).

5.7 Outcomes Research Assessments

HRQoL will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is the most commonly used QoL instrument in advanced melanoma clinical studies. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 comprises 6 functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4-point categorical scales ranging from 0 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

General health status will be measured using the EQ-5D. The EQ-5D is a standardized instrument for use as a measure of self-reported health status. The EQ-5D comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety) and a visual analog rating scale (VAS). The utility data generated from the EQ-5D is recommended for and commonly used in cost effectiveness analysis.

The EQ-5D will be administered along with the EORTC QLQ-C30 during on-study phases (Parts 1 and 2) as outlined in Section 5.1, to all subjects.

Healthcare resource utilization data (eg, hospitalizations, non-protocol specified medical visits, diagnostics, etc) will be collected for all randomized subjects. The resource utilization capture is specific to hospital admission utilization data and non-protocol specified visits related to study therapy. Resource utilization questions will be collected on-study phases (Parts 1 and 2) as outlined in Section 5.1, to all subjects.

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 6.7 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. For subjects randomized and never treated with study drug, SAEs should be collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).

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.

A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

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 until 100 days from the last dose 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.

Every adverse event must be assessed by the investigator with regard to whether it is considered immune-mediated. For events which are potentially immune-mediated, additional information will be collected on subject's case report form.

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 Immune-mediated Adverse Events

Immune-mediated adverse events (IMAEs) are AEs consistent with an immune-mediated mechanism or immune-mediated component for which non-inflammatory etiologies (eg, infection or tumor progression) have been ruled out. IMAEs can include events with an alternate etiology which were exacerbated by the induction of autoimmunity. Information supporting the assessment will be collected on the subject's case report form.

6.4 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).

6.5 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 the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the blinded study drug(s) will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of blinded study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur. Under no circumstances will dosing **during** pregnancy be allowed.

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.

6.6 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered of both excessive and specifically important.

All occurrences of overdose must be reported as SAEs (see Section 6.1.1 for reporting details).

6.7 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.

6.8 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

Not applicable to this study.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Approximately 346 subjects will be randomized to the 2 treatment arms in a 1:1 ratio in order to target 340 treated subjects (170 per arm). Given a two-sided alpha of 0.05, this number of treated subjects provides 80% power to show a statistically significant difference in the rate of drug-related Grade 3 - 5 AEs between the two treatment arms, assuming a rate of 40% in Arm A and a rate of 55% in Arm B.

We assume that treatment with N3I1 (Arm A) will result in a 15% reduction in the rate of drug-related Grade 3 - 5 events when compared to treatment with N1I3 (Arm B). The difference of 15% is clinically meaningful and assumes a 40% event rate in Arm A and a 55% event rate in Arm B. The assumption of 55% in Arm B is based on observed rates of drug-related Grade 3 - 5 AEs in the combination arm of studies CA209069 and CA209067, which enrolled the same patient population as the current study (previously untreated metastatic melanoma). The assumed reduction to 40% in Arm A corresponds to the same rate ratio (0.727) that was observed in Cohort 2a relative to Cohort 2 in Study CA209004.

Table 8.1-1 shows the precision that the sample size of 170 treated subjects per arm will provide for estimating adverse event rates (primary endpoint) or objective response rates (secondary endpoint), under different assumed observed rates.

For example, if exactly 68 of 170 treated subjects (40%) experience a drug-related Grade 3 - 5 AE in Arm A and 94 of 170 treated subjects (55.3%) experience a drug-related Grade 3 - 5 AE in Arm B, then the exact 95% CI for the rate of drug-related Grade 3 - 5 AEs will be (32.6%, 47.8%) for Arm A and (47.5%, 62.9%) for Arm B.

Furthermore, if exactly 102 of 170 treated subjects (60%) experience an objective response in a treatment arm, then the exact 95% CI for the ORR in that treatment arm will be (52.2%, 67.4%). If the observed ORR is exactly the same in each arm and equal to 60%, then the 95% CI for the difference in ORR between arms will be (-10.4%, 10.4%), and the 95% CI for the odds ratio will be (0.65, 1.54).

Table 8.1-1: Exact 95% CI for Rates when Observed in 170 Subjects

Number Subjects with Event	Observed Rate	Lower limit Exact 95% CI	Upper limit Exact 95% CI
68	40.0%	32.6%	47.8%
77	45.3%	37.7%	53.1%
85	50.0%	42.2%	57.8%
94	55.3%	47.5%	62.9%
102	60.0%	52.2%	67.4%

8.2 Populations for Analyses

Since the primary objective will be addressed by a safety endpoint, the primary endpoint analysis will be based on all treated subjects. For consistency, the secondary endpoints will use the same analysis population as the primary endpoint (ie, all treated subjects).

- All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IRT.
- All Randomized Subjects: All subjects who were randomized to any treatment group. This is the primary dataset for efficacy listings
- All Treated Subjects: All subjects who received at least one dose of any study medication**.** This is the primary dataset for analysis of study conduct, study population, efficacy (including secondary endpoints), exposure, and safety (including primary endpoint).
- PK Subjects: All treated subjects with available serum time-concentration data.
- Immunogenicity Subjects: All treated subjects with available ADA data.
- Biomarker Subjects: All treated subjects with available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint of the study is the rate of drug-related Grade 3 - 5 AEs. The drug-related Grade 3 - 5 AE rate is defined as number of subjects who experienced at least 1 AE of Grade 3 or higher, judged to be related to study drug by the investigator, and with onset on or after the first dose of study treatment and within 30 days of the last dose of study treatment, divided by number of treated subjects. AE grade will be defined using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0 criteria.

The analysis of the primary endpoint will occur when all subjects who are still on-treatment have had at least 2 post-baseline tumor assessments.

8.3.2 Secondary Endpoint(s)

Descriptive analyses of secondary endpoints will be performed to evaluate the hypothesis of similar efficacy between the treatment arms.

The first secondary endpoint is ORR as determined by investigators. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of treated subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12 following randomization, every 8 weeks for the first 12 months and then every 12 weeks until disease progression.

The second secondary endpoint is PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy.

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

The fourth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-C30 scales. HRQoL will be evaluated per Section 5.7.

Secondary endpoints will be analyzed at the time of the primary endpoint analysis.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized in all treated subjects by treatment group, as treated, using descriptive statistics.

8.4.2 Efficacy Analyses

The primary endpoint is related to safety and there are no primary efficacy endpoints. Analysis methods for the primary safety endpoint are described in Section 8.4.4.1.

8.4.2.1 Secondary Endpoints Methods

Descriptive analyses of secondary endpoints will be performed to evaluate the hypothesis of similar efficacy between the treatment arms.

ORRs and corresponding 95% exact CIs will be calculated using the Clopper Pearson method for each of the treatment arms. BOR will be tabulated for each treatment group. The 2 treatment arms will be compared using a two-sided Cochran-Mantel-Haenszel (CMH) test, stratified by PD-L1 expression and M stage at screening. Associated odds ratios and 95% CIs for Arm A relative to Arm B will be calculated, and a p-value will be presented for descriptive purposes. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology, adjusting for the stratification factors PD-L1 expression and M stage at screening.

PFS curves for each treatment group will be estimated using the Kaplan-Meier (KM) product limit method. Median PFS and corresponding two-sided, 95% confidence intervals will be computed.

Descriptive HRs and corresponding two sided 95% CIs for Arm A relative to Arm B will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status and M Stage at screening. A p-value from a 2-sided log-rank test stratified by PD-L1 expression and M stage at screening will be presented for descriptive purposes. PFS rates at 6 months with 95% CIs will be estimated using KM methodology.

OS will be summarized descriptively using Kaplan-Meier methodology. Median values, along with two-sided 95% CIs will be calculated. Additional survival analysis may be conducted for up to 5 years beyond analysis of the primary endpoint.

[redacted]

8.4.4 Safety Analyses

8.4.4.1 Primary Endpoints Methods

For the primary analysis, we will report the drug-related Grade 3 - 5 AE rate by treatment arm, the difference in rates between arms, and the corresponding 95% CIs. Two sided CMH test stratified by PD-L1 status and M Stage at screening will be performed to compare the drug-related Grade 3 - 5 AE rate between the two treatment arms.

An additional descriptive summary of drug-related AEs will be performed including only those events with onset during the combination portion (Part 1) of the regimen.

8.4.4.2 Other Safety Analysis

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

8.4.5 Pharmacokinetic Analyses

[redacted]

[redacted]

8.4.6 Biomarker Analyses

Methodology for exploratory biomarker analyses is described in the statistical analysis plan.

8.4.7 Outcomes Research Analyses

Analysis of EORTC QLQ-C30 will be performed in all patients who have an assessment at baseline and at least one follow-up assessment. All scales and single items are scored on a categorical scale and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health/quality of life and higher scores for a symptom scale representing higher level of symptoms. EORTC QLQ-C30 scale data will be summarized by timepoint using descriptive statistics for each treatment group

8.4.8 Other Analyses

Methodology for other analyses including immunogenicity, other HRQoL questionnaires, and healthcare resource utilization is described in the statistical analysis plan.

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). 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:

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

The data collected during this study are confidential and proprietary to 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 contraception's must be discussed in the event that the subject chooses to forego complete abstinence.

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	Anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
AJCC	American Joint Committee on Cancer
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransaminases
β-HCG	beta-human chorionic gonadotrophin
BMS	Bristol-Myers Squibb
BOR	Best overall response
BORR	best overall response rate
BP	blood pressure
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
Ca++	calcium
Cavg	average concentration
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
C1-	chloride
CLcr	creatinine clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CR	Complete response
CRC	Colorectal Cancer

Term	Definition
CRF	Case Report Form, paper or electronic
CT	Computerized tomography
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
dL	deciliter
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eg	exempli grata (for example)
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality Of Life Questionnaire-core 30
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
g	gram
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation
ICC	investigator's choice of chemotherapy
ie	id est (that is)
IEC	Independent Ethics Committee
IL	interleukin
IMAE	Immune-mediated adverse event
IMP	investigational medicinal products

Term	Definition
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IRT	Interactive Response Technologies web-based system
IU	International Unit
IV	intravenous
K+	potassium
kg	kilogram
L	liter
LDH	lactate dehydrogenase
mg	milligram
Mg++	magnesium
min	minute
mL	milliliter
mRCC	Metastatic renal cell carcinoma
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AE
NE	Not evaluable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall survival
PD	pharmacodynamics
PD	Progressive disease
PD-1	Programmed death-1

Term	Definition
PD-L1	Programmed cell death- ligand 1
PD-L2	Programmed cell death- ligand 2
PFS	Progression free survival
PK	pharmacokinetics
PPK	population pharmacokinetic
PR	Partial response
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SD	Stable disease
SNP	Single nucleotide polymorphism
SOP	Standard Operating Procedures
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
Tmax, TMAX	time of maximum observed concentration
TTR	Time to response
ULN	Upper limit of normal
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential