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Clinical Protocol CA209064

An Open-Label, Randomized, Phase 2 Study of Nivolumab Given Sequentially with Ipilimumab in Subjects with Advanced or Metastatic Melanoma

(**CheckMate 064**: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **064**)

Revised Protocol Number: 01
Incorporates Amendment: 04 and Administrative Letter 01

Medical Monitor / Study Director
Allen Chen, MD
[redacted]

protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 01	28-Mar-2013	Incorporates Amendment 04 and Administrative Letter 01.
Amendment 04	28-Mar-2013	Inclusion of pre-clinical safety findings related to reproductive toxicology data. Added Guidance on Contraception Appendix. Added CheckMATE protocol number to the study title. [redacted]
Administrative Letter 01	11-Feb-2013	Clarifies that the investigational product nivolumab is also known as BMS-936558 and in Table 4.1-1the product description and dosage form is labeled as BMS-936558-01.
Original Protocol	07-Jan-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209064

Protocol Title: CA209-064: An Open-Label, Randomized, Phase 2 Study of Nivolumab Given Sequentially with Ipilimumab in Subjects with Advanced or Metastatic Melanoma **(CheckMate 064: CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation **064)**

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab (BMS-936558) at 3 mg/kg every 2 weeks for up to 6 doses in Induction Period. Ipilimumab at 3 mg/kg every 3 weeks for up to 4 doses in Induction Period. Nivolumab at 3 mg/kg every 2 weeks in Continuation Period until progression, unacceptable toxicity, or withdrawal of consent, for a maximum duration of 2 years from first study treatment in Induction Period 1.

Study Phase: 2

[redacted]

Objectives:

Primary Objective:

- To evaluate the incidence of treatment-related Grade 3 - 5 AEs during the Induction Period in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipiliumuab followed by nivolumab

Secondary Objectives:

- To evaluate the response rate at Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab
- To evaluate progression rates at Week 13 and Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab

[redacted]

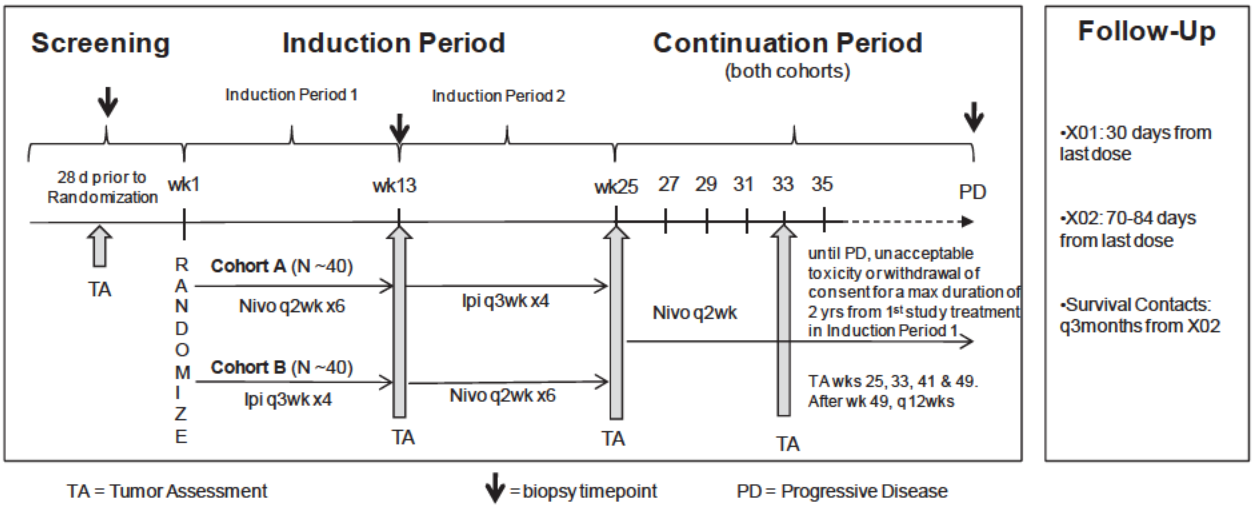
Study Design:

This is an open-label, randomized, Phase 2 study of two schedules of nivolumab given sequentially with ipilimumab, in adult (≥ 18 years old) male and female subjects with advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Approximately 80 subjects will be randomized (1:1) to receive one of two dosing schedules (Cohort A or B). Randomization will stay open until at least 40 subjects in each Cohort have been treated with at least one dose of study treatment in Induction Period 1 and 35 subjects in each Cohort have received at least one dose of study treatment in Induction Period 2.

Subjects may be treatment-naive or have experienced disease recurrence or progression after one prior systemic therapy (prior immunotherapy with anti-PD1 or anti-CTLA-4 is prohibited). The two dosing schedules to be explored are presented in Figure 1.

Accrual duration is expected to be around 1 year. Primary and secondary endpoint analysis will be performed when at least 40 subjects per cohort have completed/discontinued Induction Period 1 and at least 35 subjects per cohort have completed/discontinued Induction Period 2, and all treated subjects with an objective response at Week 25 have been followed through study Week 33 in order to confirm disease response. This will take place after a maximum of 32 weeks after last patient first treatment date. An update of OS analysis is planned after 65% of the subjects have died or 2 years of follow-up time from last subject randomized, whichever comes first. Assuming a median OS of 20 months for both cohorts, approximately 65% of the subjects would have died after a 12 months accrual period followed by a two years of follow-up time.

Figure 1: Study Design Schematic



Study Population:

Key Inclusion Criteria:

- Subjects with histologically confirmed unresectable Stage III or Stage IV melanoma
- Subjects may be treatment-naive, or have experienced disease recurrence or progression during or after one prior systemic regimen for advanced disease
- Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria. (radiographic tumor assessment must be performed within 28 days prior to randomization.)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix 1)
- 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
- Subjects must have sufficient tumor tissue accessible for baseline and post-treatment biopsies (core needle or excisional). The site of tumor biopsy should not be the only site of measurable disease.

Key Exclusion Criteria:

- Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated with surgery and/or radiation therapy, and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) and neurologically and radiographically stable for at least 6 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 14 days prior to study treatment.
- Subjects with carcinomatous meningitis

- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
- Subjects who received prior treatment with other immunotherapies (eg, antibodies, vaccines, adoptive T-cell transfer), must have experienced disease progression at least 6 weeks prior to first dose of study treatment and, with the exception of IL-2 or adjuvant interferon, must be discussed and approved by the Medical Monitor prior to signing informed consent
- Prior therapy with BRAF inhibitor (eg, vemurafenib)

Study Assessments & Endpoints: The primary endpoint of the study is the rate of treatment-related Grade 3-5 AEs during the Induction Period (Periods 1 and 2) in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab.

The treatment-related Grade 3 - 5 AEs rate is defined as number of subjects who experienced at least 1 treatment related Grade3 - 5 adverse event (per NCI CTCAE v 4.0 criteria, any PT terms) with an onset date after or on first day of the induction period and not later than discontinuation date from the Induction Period, divided by number of treated subjects. AEs with an onset date after start of subsequent anti-cancer therapy, or start date of Continuation Period treatment will not be included. For subjects who discontinue Induction Period early and enter the Follow-Up Period, AEs that occur in Follow-Up, including those before Week 25, will not be included in the primary endpoint. For subjects who discontinue treatment before the end of Induction Period 1 or 2 but who are eligible to enter the next study period, AEs that occur before end of Induction Period 2 will be included in the primary endpoint, even if they occur after dosing ends while they are waiting to enter the next study period.

The secondary endpoints are Response Rate at Week 25 and Progression Rates at Weeks 13 and 25. Subjects will be assessed for response via tumor assessments (CT or MRI) prior to dosing at Weeks 13, 25, 33, 41, 49 (+/- 1 weeks) and then every 12 weeks. Response rate at Week 25 is defined as the number of subjects who have a complete response (CR) or partial response (PR) at Week 25 (regardless of the tumor assessment at Week 13), with confirmation at scheduled scan at Week 33, divided by the total number of randomized subjects. Progression rates at Weeks 13 and 25 are defined as the number of subjects who have Progressive Disease (PD) per RECIST 1.1 at the specific timepoint (Week 13 or Week 25) divided by the total number of randomized subjects.

Statistical Considerations:

Sample Size: This trial is an estimation trial. Sample size in this study will be approximately 40 subjects per cohort and is not based on power considerations. Tables below provide the 95% confidence intervals computed from different observed rates. Those tables indicate what would be the reliability of the AE rate estimates for N=40 (Table 8.1-1) and N=35 (Table 8.1-2) treated subjects. A threshold of 45% will be applied to the upper limit of the confidence interval as an informal guideline for high toxicity

Thirty-five subjects per cohort will be the minimum number of subjects receiving treatment in Induction Period 2. For that purpose, randomization will stay open until at least 40 subjects in each cohort have been treated with at least one dose of study treatment in Induction Period 1 and 35 subjects in each cohort have received at least one dose of study treatment in Induction Period 2. Assuming a drop-out rate during induction period 1 would be at most 12.5%, at least 35 subjects would be treated in induction period 2 if 40 subjects are to be randomized per cohort.

Analyses:

Primary analysis:

Rate of treatment-related Grade 3-5 AEs during the induction period will be computed by treatment cohort using all treated subjects. Corresponding 95% CIs will be calculated using the Clopper-Pearson method. As sensitivity analysis, rates and 95% CI will be also computed using the subset of subjects who received at least one dose of study treatment in Induction Period 2.

Secondary analyses:

Response rate at Week 25 will be computed by treatment arm using all randomized subjects. Response rate estimates and corresponding 95% CIs will be calculated using the Clopper-Pearson method. Response rates including only those subjects who had a tumor assessment at Week 25 will also be computed. Duration of response from Week 25 will be assessed for subjects with confirmed response at Week 25. Median DOR estimate and corresponding 95% CIs will be provided for each sequential induction regimen using the Kaplan-Meier methodology. Progression rate estimates at Week 13 and Week 25 along with corresponding 95% CIs will be calculated using the Clopper-Pearson method.

TABLE OF CONTENTS

1 INTRODUCTION [redacted]

[redacted]

[redacted]

1.3 Objective(s)

1.3.1 Primary Objective

- To evaluate the incidence of treatment-related Grade 3-5 AEs during the Induction Period in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipiliumuab followed by nivolumab

1.3.2 Secondary Objectives

- To evaluate the response rate at Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab
- To evaluate progression rates at Week 13 and Week 25 in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab

[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 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 are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

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

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

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

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

3 INVESTIGATIONAL PLAN

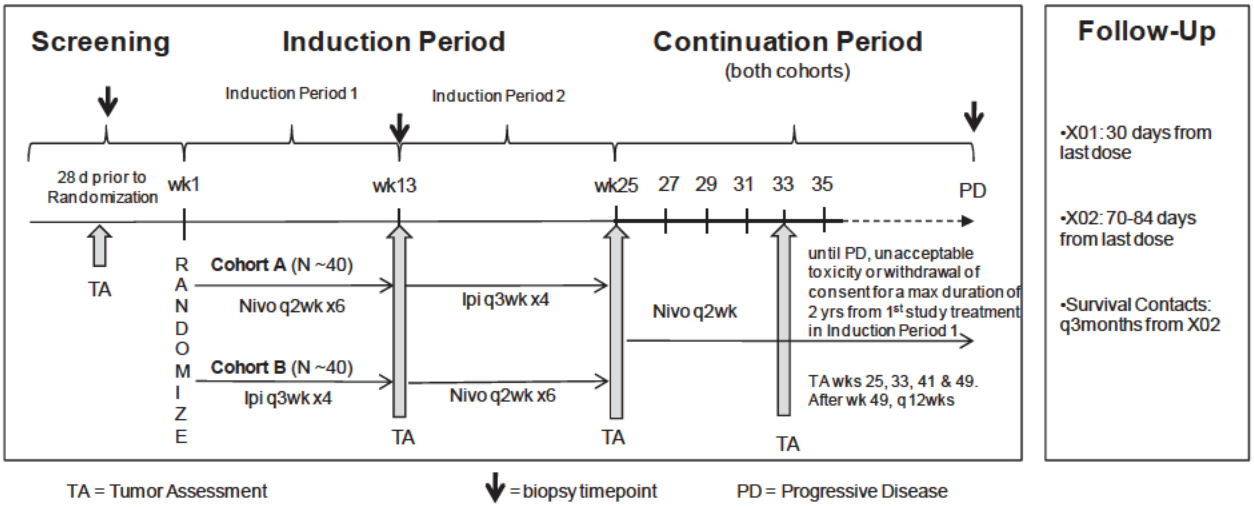
3.1 Study Design and Duration

This is an open-label, randomized Phase 2 study of two schedules of nivolumab given sequentially with ipilimumab, in adult (≥ 18 years old) male and female subjects with advanced (unresectable Stage III) or metastatic (Stage IV) melanoma. Approximately 80 subjects will be randomized (1:1) to receive one of two dosing schedules (Cohort A or B).

Randomization will stay open until at least 40 subjects in each Cohort have been treated with at least one dose of study treatment in Induction Period 1 and 35 subjects in each Cohort have received at least one dose of study treatment in Induction Period 2.

Subjects may be treatment-naive or have experienced disease recurrence or progression after one prior systemic therapy (prior immunotherapy with anti-PD1 or anti-CTLA-4 is prohibited). The two dosing schedules to be explored are presented in Figure 3.1-1.

Figure 3.1-1: Study Design Schematic



Subjects in Cohort A will receive nivolumab at 3 mg/kg every 2 weeks for up to 6 doses during Weeks 1 to 13 in Induction Period 1, followed by ipilimumab at 3 mg/kg every 3 weeks for up to 4 doses during Weeks 13 to 25 in Induction Period 2. Subjects in Cohort B will receive the reciprocal sequence.

During Induction Periods 1 and 2, doses of either nivolumab or ipilimumab may be omitted if there is an AE which precludes treatment at a scheduled treatment visit (Section 4.3.4.1). Dose delays, reductions, and escalations are not permitted for either nivolumab or ipilimumab. Dose interruptions will be allowed for infusion reactions, according to guidelines in Section 4.3.4. After completion of Induction Period 2, eligible subjects in both cohorts will enter the Continuation Period and receive nivolumab at 3 mg/kg every 2 weeks until progression, unacceptable toxicity, or withdrawal of consent. The maximum duration of treatment to be administered to an individual subject in this study is 2 years from the first study treatment in Induction Period 1. Additional ipilimumab treatment during the Continuation Period will not be allowed.

Tumor assessments will be obtained prior to dosing, as applicable, at the targeted weeks (Table 5.1-1, Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5). Tumor response will be evaluated at the end of Induction Period 1 (Week 13) and at the end of Induction Period 2 (Week 25), then Week 33 and Week 41, and then every 12 weeks starting at Week 49, using RECIST version 1.1. Before treatment in the Continuation Period can begin, the tumor assessment at the end of

Induction Period 2 must be reviewed to determine if the subject meets any of the exception criteria in Section 3.1.2.3. During the Continuation Period, each tumor assessment must be reviewed before the next dose of nivolumab can be given.

In the Continuation Period, subjects will be permitted to continue nivolumab treatment beyond initial RECIST 1.1-defined progression if they are assessed by the investigator to be deriving clinical benefit, are tolerating study treatment, and provide informed consent (see Section 4.3.5). Such subjects should discontinue study treatment upon evidence of further progression.

This study will consist of 3 phases: Screening, Treatment (Induction Period 1, Induction Period 2, and Continuation Period), and Follow-Up.

3.1.1 Screening

- Begins by establishing subject's initial eligibility and signing of the informed consent.).
- Subject is enrolled using the Interactive Voice Response System (IVRS). This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented.
- Subject is assessed for complete study eligibility within 28 days prior to randomization (Table 5.1-1).
- Subjects meeting all eligibility criteria must undergo a fresh tumor biopsy (Section 5.6.1), ECG, and whole blood collection for SNP assessment.

3.1.2 Treatment Phase (Induction Period 1, Induction Period 2, Continuation Period)

- Begins with the randomization call to the IVRS. The subject is randomly assigned to either Cohort A or Cohort B.
- Doses of either nivolumab or ipilimumab may be omitted if there is an AE which precludes treatment at a scheduled treatment visit (Section 4.3.4.1). Treatment may resume at the next scheduled dose if retreatment criteria (specified in Section 4.3.4.2) are met.
- Dose interruptions will be allowed for infusion reactions, according to guidelines in Section 4.3.4.3.
- Tumor biopsies (Section 5.6.1) must be performed at Week 13 and time of disease progression, unless the designated lesion(s) have responded during study treatment and are no longer accessible for biopsy.
- Treatment Phase ends when subject completes or discontinues all study dosing.

3.1.2.1 Induction Period 1

- Induction Period 1 begins at Week 1, Day 1. Induction Period 1 is the first 12 weeks of study treatment (Week 1 to Week 13). Subjects must receive the first dose of study treatment within 3 working days following randomization.

  - Subjects in Cohort A will receive nivolumab at a dose of 3 mg/kg as a 60 minute IV infusion every 2 weeks (14 days) for up to 6 doses.
  - Subjects in Cohort B will receive ipilimumab at a dose of 3 mg/kg as a 90 minute IV infusion every 3 weeks (21 days) for up to 4 doses.
- Study assessments will be conducted as outlined in Table 5.1-2 and Table 5.1-3.
- Tumor biopsies (Section 5.6.1) must be performed prior to dosing at Week 13, unless the designated lesion(s) have responded during study treatment and are no longer accessible for biopsy.
- All subjects must have tumor assessment performed at Week 13 (prior to the first dose in Induction Period 2). This includes any subject who may have discontinued treatment prior to receiving all planned Induction Period 1 doses.
- Subjects who have clinical or radiographic progressive disease prior to the completion of Induction Period 1 are to remain on their current study treatment for the remainder of Induction Period 1, provided they are tolerating study treatment and do not have rapid clinical deterioration.
- Subjects who do not receive all planned doses in Induction Period 1, including those who discontinue Induction Period 1 treatment early due to progression or discontinuation criteria (Section 4.3.6.2), are to continue their scheduled study assessments (as per Table 5.1-2 and Table 5.1-3) and are still eligible to receive the alternative treatment in Induction Period 2, starting at Week 13.
- After completion of Induction Period 1, subjects will proceed to Induction Period 2, regardless of the results of the tumor assessment at the end of Induction Period 1.

3.1.2.2 Induction Period 2

- Induction Period 2 begins at Week 13 and continues to Week 25.
  - Subjects in Cohort A will receive ipilimumab at a dose of 3 mg/kg as a 90 minute IV infusion every 3 weeks (21 days) for up to 4 doses.
  - Subjects in Cohort B will receive nivolumab at a dose of 3 mg/kg as a 60 minute IV infusion every 2 weeks (14 days) for up to 6 doses.
- Subjects with drug-related AEs after the last dose in Induction Period 1 who fail to meet retreatment criteria (Section 4.3.4.2) at Week 13 will still begin Induction Period 2 at Week 13 and require omission of the initial dose(s) in Induction Period 2 until retreatment criteria are met.
- Study assessments will be conducted as outlined in Table 5.1-2 and Table 5.1-3.
- All subjects, including those who discontinue study treatment prior to receiving all planned doses during Induction Period 2, must have a tumor assessment at Week 25 (after the last dose of Induction Period 2 and prior to the first dose of the Continuation Period).
- Subjects who have clinical or radiographic progressive disease prior to the completion of Induction Period 2 are to remain on their current study treatment for the remainder of Induction Period 2, provided they are tolerating study treatment and do not have rapid clinical deterioration.

- Subjects who do not receive all planned treatment doses in Induction Period 2, including those who discontinue Induction Period 2 treatment early due to progression or discontinuation criteria in Section 4.3.6.2, are to continue their scheduled study assessments (as per Table 5.1-2 and Table 5.1-3) and may still be eligible to receive treatment in the Continuation Period, starting at Week 25.

3.1.2.3 Continuation Period

- Beginning at Week 25, subjects in both cohorts will enter the Continuation Period and receive nivolumab at 3 mg/kg every 2 weeks until progression, unacceptable toxicity, or withdrawal of consent **with the following exceptions** below. Note that only the protocol-specified tumor assessments at the end of Induction Period 1 and 2 are considered in these exceptions.
  - Subjects who met treatment discontinuation criteria during prior nivolumab treatment in Induction Period 1 or 2 (see Section 4.3.6.2) may not receive additional nivolumab treatment in the Continuation Period.
  - Subjects in both Cohorts A and B who had progression on the tumor assessment at the end of Induction Period 1 and have an additional 20% or greater increase in the sum of longest diameters, including all target lesions and measurable new lesions, on the tumor assessment at the end of Induction Period 2, will be discontinued from study treatment and not permitted to proceed to the Continuation Period.
  - Subjects in Cohort A who had progression on the tumor assessment at the end of Induction Period 1 but do not have an additional 20% or greater increase in the sum of longest diameters (including all target lesions and measurable new lesions) on the tumor assessment at the end of Induction Period 2 may, at the discretion of the investigator, either proceed to treatment in the Continuation Period or be discontinued from study treatment if the investigator feels that the subject is not likely to benefit from nivolumab treatment in the Continuation Period. Such Cohort A subjects must also meet the criteria for treatment beyond disease progression, as specified in Section 4.3.5.
  - Subjects in Cohort B who did not have progression on the tumor assessment at the end of Induction Period 1 but who do have progression on the tumor assessment at the end of Induction Period 2 may, at the discretion of the investigator, either be discontinued from study treatment or proceed to nivolumab reatment in the Continuation Period, provided they meet the criteria for treatment beyond progression, as specified in Section 4.3.5
- Study assessments will be conducted as outlined in Table 5.1-4.
- The maximum duration of treatment to be administered to an individual subject in this study is 2 years from the first study treatment in Induction Period 1.
- Additional ipilimumab treatment during the Continuation Period is not allowed.
- In the Continuation Period, nivolumab may be continued beyond initial evidence of progression if criteria specified in Section 4.3.5 are met. For subjects who continue nivolumab beyond initial progression, a subsequent tumor assessment must be performed 4 to 8 weeks later. Treatment must be discontinued upon evidence of further progression (see Section 4.3.5).

- For subjects who begin the Continuation Period with RECIST 1.1-defined progression based on their tumor assessment at the end of Induction Period 2 and who receive treatment beyond progression in the Continuation Period, the protocol specified tumor assessment at Week 33 may serve as the subsequent assessment.
- Tumor assessments will be performed prior to dosing on Weeks 33 and 41, then every 12 weeks (prior to dosing) starting at Week 49.

3.1.3 Follow-Up Period

- Begins when the decision is made to discontinue a subject from study treatment or the subject has completed 2 years of study therapy from the first study treatment in Induction Period 1 (no further treatment with either nivolumab or ipilimumab)
- For subjects who have NOT progressed, tumor assessments will continue as scheduled at Weeks 13, 25, 33, 41 and then starting at Week 49 every 12 weeks until documented progression.
- Subjects will be followed for all toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All AEs will be documented for a minimum of 100 days after last dose of study treatment.

After completion of the two "X" follow-up visits (Table 5.1-5) subjects will be followed every 3 months (by clinic visit or telephone contact) for survival and report of any subsequent anti-cancer treatments for up to 5 years from the first dose of study treatment in Induction Period 1 until death, loss to follow-up, or withdrawal of consent.

3.1.4 Study Duration

Accrual duration is expected to be around 1 year; overall study duration will be approximately 6 years.

Primary and secondary endpoint analysis is expected to be performed approximately at 20 months from the date of first patient first treatment. This will occur when at least 40 subjects per cohort have completed/discontinued Induction Period 1 and at least 35 subjects per cohort have completed/discontinued Induction Period 2 and all treated subjects with an objective response at Week 25 have been followed through study Week 33 in order to confirm disease response. This will take place after a maximum of 32 weeks after last patient first treatment date.

An update of OS analysis is expected to be performed at 36 months (12 months accrual + 2 years follow-up). This update of OS analysis is planned to occur after 65% of the subjects have died or 2 years of follow-up time from last subject randomized, whichever comes first. Assuming a median OS of 20 months for both cohorts, approximately 65% of the subjects would have died after a 12 months accrual period followed by a two years of follow-up time.

Additional survival follow-up may continue for up to 5 years from the first dose of study treatment in Induction Period 1. Additional OS analysis may be conducted periodically until end of study. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug (nivolumab). 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 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, tumor biopsies, and other requirements of the study.

2. Target Population

a) Subjects with histologically confirmed unresectable Stage III or Stage IV melanoma

b) Subjects may be treatment-naive, or have experienced disease recurrence or progression during or after one prior systemic regimen for advanced disease

i) Specific prior immunotherapy regimens, including prior treatment with anti-PD-1 or anti-CTLA-4 directed agents, are excluded (see Exclusion criteria for details)

ii) Documented recurrence of Stage III unresectable or Stage IV melanoma after prior neo-adjuvant or adjuvant interferon is allowed

iii) Previously treated subjects must have completed their prior regimen > 4 weeks before the first dose of study treatment

c) Subjects must have measurable disease by CT or MRI per RECIST 1.1 criteria. (radiographic tumor assessment must be performed within 28 days prior to randomization.)

d) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (refer to Appendix 1)

e) Subjects must have 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.

f) Subjects must have sufficient tumor tissue accessible for baseline and post-treatment biopsies (core needle or excisional). The site of tumor biopsy should not be the only site of measurable disease.

   i) Lesions should not have received prior radiation therapy

   ii) These sites must be designated for biopsy prior to the first treatment, to avoid selection bias that may affect study endpoints.

   iii) Pathologic confirmation of viable tumor cells from collected tissue samples is strongly recommended to permit consideration of repeat biopsy if deemed of acceptable clinical risk.

g) All baseline laboratory requirements will be assessed and should be obtained within 14 days of randomization. Screening laboratory values must meet the following criteria

   i) WBCs ≥ 2000/μL

   ii) Neutrophils ≥ 1500/μL

   iii) Platelets ≥ 100 x 10^3/μL

   iv) Hemoglobin ≥ 9.0 g/dL

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

   vi) AST ≤ 3 x ULN

   vii) ALT ≤ 3 x ULN

   viii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome who must have total bilirubin < 3.0 mg/dL)

h) Prior focal radiotherapy to an isolated bony or soft tissue metastasis must be completed at least 2 weeks before study drug administration. Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site. No radiopharmaceuticals (eg, strontium, samarium) within 8 weeks before study drug administration

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

3. Age and Reproductive Status

a) Men and women ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in Appendix 2. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly

effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives.

There is an insufficient amount of information to assess the teratogenicity for nivolumab. The half-life of nivolumab is up to 25 days; therefore, WOCBP who received nivolumab should use an adequate method to avoid pregnancy for 23 weeks after the last dose of nivolumab.

There is no data assessing the teratogenicity for ipilimumab. The half-life of ipilimumab is 14.7 days; therefore, WOCBP who received ipilumumab should use an adequate method to avoid pregnancy for 15 weeks after the last dose of ipilimumab.

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

d) Women must not be breastfeeding

e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year (as indicated on the Informed Consent Form). The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half lives.

The half-life of nivolumab is up to 25 days; therefore, men who received nivolumab and are sexually active with WOCBP must continue contraception for 31 weeks after the last dose of nivolumab.

The half-life of ipilimumab is 14.7 days ; therefore, men who received ipilimumab and are sexually active with WOCBP must continue contraception for 24 weeks after the last dose of ipilimumab.

f) Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile; see Section 3.3.3 for the definition of WOCBP) and azoospermic men do not require contraception.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Subjects with active CNS metastases are excluded. Subjects are eligible if CNS metastases are adequately treated with surgery and/or radiation therapy, and subjects are neurologically returned to baseline (except for residual signs or symptoms related to the CNS treatment) and neurologically and radiographically stable for at least 6 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or

decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 14 days prior to study treatment.

b) Subjects with carcinomatous meningitis

2. Medical History and Concurrent Diseases

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

b) Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

c) Prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).

d) Subjects who received prior treatment with other immunotherapies (eg, antibodies, vaccines, adoptive T-cell transfer), must have experienced disease progression at least 6 weeks prior to first dose of study treatment and, with the exception of IL-2 or adjuvant interferon, must be discussed and approved by the Medical Monitor prior to signing informed consent

e) Prior therapy with BRAF inhibitor (eg, vemurafenib)

f) All toxicities attributed to prior anti-cancer therapy other than alopecia and fatigue must have resolved to grade 1 (NCI CTCAE version 4) or baseline before administration of study drug.

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

h) Subjects with previous malignancies (except non-melanoma skin cancers, in situ bladder cancer, gastric or colon cancers, cervical cancers/dysplasia, or breast carcinoma in situ) are excluded unless a complete remission was achieved at least 2 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.

i) Known drug or alcohol abuse

j) Any serious or uncontrolled medical disorder or active infection that, in the opinion of the investigator, may increase the risk associated with study participation, study drug administration, or would impair the ability of the subjet to receive protocol therapy.

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus surface antigen (HBVsAg) or hepatitis C virus ribonucleic acide (HCV RNA) indicating acute or chronic infection.

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

4. Allergies and Adverse Drug Reaction

a) History of Grade ≥ 3 allergy to study drug components.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding.

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

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

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) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In addition, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

[redacted]

[redacted]

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- **Additional protocol specific reasons for discontinuation (see Section 4.3.6)**

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

If study treatment 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 Treatment Study Follow up

In this study, Overall Survival is an important exploratory endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 -

Study Assessments and Procedures for up to 5 years from the first dose of study treatment in Induction Period 1 until death, lost to follow-up, or withdrawal of consent.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by 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. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

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

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

4.1 Study Treatments

Table 4.1-1: Product Description - Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936588-01 Solution for Injection	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid. May contain particles.	2 to 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear, colorless liquid. May contain particles	2 to 8°C. Protect from light and freezing.

4.1.1 Investigational Product

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

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

In this protocol, investigational product(s) is/are: BMS-936558 (nivolumab) and ipilimumab.

4.1.2 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.

In this protocol, non-investigational product(s) is/are: Not applicable.

4.1.3 Handling and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets). Refer to the BMS-936558 (nivolumab) investigator brochure or ipilimumab package insert for details related to handling and dose preparation, as well as any pharmacy instruction sheets.

For non-investigational product, if marketed product is utilized, it should be stored in accordance with the package insert, summary of product characteristics (SmPC), or similar.

4.2 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS 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 IVRS, enrolled subjects that have signed the informed consent form and met all eligibility criteria will be randomized through the IVRS. The following information is required for subject randomization:

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

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Cohort A (nivolumab followed by ipilimumab) or Cohort B (ipilimumab followed by nivolumab).

4.3 Selection and Timing of Dose for Each Subject

Dosing calculations should be based on the body weight assessed at each visit as per Table 5.1-2, Table 5.1-3, and Table 5.1-4. All doses should be rounded to the nearest milligram. There will be no nivolumab or ipilimumab dose escalations or reductions permitted.

The first dose of study drug will be administered on Week 1, Day 1. Subsequent doses are to be scheduled from the calendar date of the first dose and have a +/- 3 day dosing window. Please refer to Table 5.1-2 and Table 5.1-3 for the appropriate timing of doses (in terms of number of Weeks/Days from first dose) in the Induction Period.

After each nivolumab dose, the next dose of study treatment may be given no sooner than 12 days later. After each ipilimumab dose, the next dose of study treatment may be given no sooner than 19 days later.

There are no premedications recommended for nivolumab or ipilimumab. Subjects should be carefully monitored for infusion reactions during nivolumab and ipilimumab administration. If an infusion reaction is noted, subjects should be managed according to Section 4.3.4.3.

There will be no dose delays permitted in this study. Doses of nivolumab or ipilimumab will be omitted if omission criteria, described in Section 4.3.4.1, are met. Treatment may resume at the next scheduled dose if retreatment criteria (specified in Section 4.3.4.2) are met.

The maximum duration of study treatment to be administered to an invididual subject is 2 years from the first study treatment in Induction Period 1.

4.3.1 Induction Period 1

Induction Period 1 will be the first 12 weeks of study treatment (Weeks 1 to 13).

- Subjects in Cohort A will receive nivolumab at a dose of 3 mg/kg as a 60 minute IV infusion every 2 weeks (14 days) for up to 6 doses.
- Subjects in Cohort B will receive ipilimumab at a dose of 3 mg/kg as a 90 minute IV infusion every 3 weeks (21 days) for up to 4 doses.

4.3.2 Induction Period 2

After completion of Induction Period 1, subjects will proceed to Induction Period 2 (12 weeks duration, from Week 13 to 25), regardless of the results of the tumor assessment at the end of Induction Period 1.

- Subjects in Cohort A will receive ipilimumab at a dose of 3 mg/kg as a 90 minute IV infusion every 3 weeks (21 days) for up to 4 doses.
- Subjects in Cohort B will receive nivolumab at a dose of 3 mg/kg as a 60 minute IV infusion every 2 weeks (14 days) for up to 6 doses.

4.3.3 Continuation Period

- Subjects in both Cohorts A and B will receive nivolumab at a dose of 3 mg/kg as a 60 minute IV infusion every 2 weeks (14 days), starting at Week 25 until disease progression, unacceptable toxicity, or withdrawal of consent, for a maximum duration of up to 2 years from the first study treatment in Induction Period 1.

4.3.4 Dose Modifications for Nivolumab and Ipilimumab

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, dose omissions) will be based on specific laboratory and AE criteria.

In some cases, the natural history of AEs associated with immunotherapy can differ and be more severe than AEs caused by other therapeutic classes. Early recognition and management may mitigate severe toxicity. The following Recommended Management Algorithms for nivolumab were developed to assist investigators and can be found in the BMS-936558 (nivolumab) Investigator Brochure:

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

In addition, the ipilimumab Investigator Brochure[5] includes Management Algorithms for the following adverse reactions:

- GI Toxicity
- Hepatotoxicity
- Skin Toxicity
- Endocrinopathy
- Neurological Toxicity
- Other immune-mediated adverse reactions, including ocular manifestations

It should be noted that beginning with the first dose of Induction Period 2, adverse events may be related to the drug given in Induction Period 2, the prior drug given in Induction Period 1, or to both drugs. Therefore, it is recommended that the Management Algorithms in both the BMS-936558 (nivolumuab) Investigator Brochure and the ipilimumab Investigator Brochure be consulted for assistance with managing adverse events after the beginning of Induction Period 2.

4.3.4.1 Dose Omissions for Nivolumab or Ipilimumab

Doses of nivolumab or ipilimumab should be omitted (not delayed) if any of the following criteria are met:

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

If the criteria to resume treatment (specified in Section 4.3.4.3) are met within the dosing window (Week X ± 3 days), then the dose may be given.

4.3.4.2 Criteria to Resume Treatment with Nivolumab or Ipilimumab

Subjects may resume treatment with nivolumab or ipilimumab when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of Grade 2 fatigue

- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline AST/ALT or total bilirubin in the Grade 1 toxicity range who require dose omissions for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If dosing is interrupted > 6 weeks, the subject must be permanently discontinued from study treatment with that particular drug, except as specified in Section 4.3.6.2.

4.3.4.3 Treatment of Infusion Reactions Related to Nivolumab or Ipilimumab

Infusion reactions related to nivolumab or ipilimumab may occasionally occur, manifested by fever, chills, rigors, headache, rash, pruritus, arthalgias, hypotension, hypertension, bronchospasm, or other allergic-like reactions. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the study medical monitor and reported as an SAE if it meets the criteria. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

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

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

Stop the nivolumab or ipilimumab 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 therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit.

For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab 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).

4.3.5 Nivolumab Treatment Beyond Disease Progression

As described in Section 1.4.4.4, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).

From the beginning of the Continuation Period, subjects will be permitted to continue or resume treatment with nivolumab beyond initial RECIST 1.1-defined PD, as long as they meet all of the following criteria:

- Investigator-assessed clinical benefit
- Subject has tolerated prior nivolumab
- Stable or improved performance status
- Treatment beyond progression will not delay an intervention to prevent imminent serious complications of disease progression (eg, CNS metastases)
- Subject provides written informed consent prior to receiving additional nivolumab treatment, using an ICF describing any reasonably foreseeable risks or discomforts and other alternative treatment options

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued nivolumab treatment.

Note that subjects with PD on any tumor assessment prior to the end of Induction Period 2 but not also on the tumor assessment at the end of Induction Period 2 (when compared to the baseline tumor assessment) are not considered to be continuing or resuming treatment beyond PD at the time of the beginning the Continuation Period.

All decisions to continue nivolumab treatment beyond initial PD must be discussed with the BMS Medical Monitor and documented in the study records.

For subjects who enter the Continuation Period with RECIST 1.1-defined PD on the tumor assessment at the end of Induction Period 2, this tumor assessment will be considered as the one documenting initial PD (even if PD was also documented on the tumor assessment at the end of Induction Period 1 or on any unscheduled tumor assessment prior to the one at the end of Induction Period 2). For subjects who enter the Continuation Period without prior evidence of PD, the first tumor assessment during the Continuation Period that documents PD will be considered the one documenting initial PD.

A radiographic tumor assessment must be performed 4 to 8 weeks after the assessment documenting initial PD. (Subjects who begin the Continuation Period with RECIST 1.1-defined progression on their tumor assessment at the end of Induction Period 2 may use the protocol specified tumor assessment at Week 33 as the subsequent assessment.) Subjects must discontinue study treatment upon evidence of **further progression**, defined as an additional 10% or greater increase in tumor burden from the time of initial PD (including all target lesions and new measurable lesions). If further progression is not documented on this next tumor assessment, then study treatment may continue until there is evidence of further progression on any subsequent tumor assessment.

New lesions are considered measurable at the time of initial PD 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-measurable at the time of initial PD may become measurable and therefore included in the tumor burden measurement if the longest diameter increases to at least 10 mm (except for pathological lymph nodes, which must have an increase in short axis to at least 15 mm).

For statistical analyses that include the investigator-assessed progression date, subjects who continue nivolumab treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered to have investigator-assessed progressive disease at the time of the initial progression event.

The criteria mentioned above, including the requirement for informed consent, **do not apply** to continued nivolumab or ipilimumab treatment in Induction Period 1 or Induction Period 2 beyond clinical or radiographic progression observed prior to the completion of those periods.

4.3.6 Nivolumab and/or Ipilimumab Treatment Discontinuation Criteria

4.3.6.1 Permanent Discontinuation Criteria for Both Nivolumab and Ipilimumab

All further study treatment (both nivolumab and ipilimumab) must be permanently discontinued if any of the following occurs during treatment with either nivolumab or ipilimumab:

Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation

- Grade 4 neutropenia ≤ 7 days
- Grade 4 lymphopenia or leukopenia
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any drug-related adverse event which requires treatment with any immunosuppressive therapy other than corticosteroids (eg, infliximab, mycophenylate)
- 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 dosing of nivolumab or ipilimumab
- Clinical or radiographic progression associated with rapid clinical deterioration which, in the judgment of the Investigator, is unlikely to benefit from further study treatment (nivolumab or ipilimumab).

4.3.6.2 Permanent Discontinuation Criteria for One Study Treatment (Discontinuation of Nivolumab Only or Discontinuation of Ipilimumab Only)

If any of the following occurs during treatment with either nivolumab or ipilimumab, treatment with **that particular drug** must be permanently discontinued:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reactions, and infusion reactions:
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
- Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

- Any drug-related liver function test (LFT) abnormality that meets the following criteria requires discontinuation:
  - AST or ALT > 5-10 x ULN for > 2 weeks
  - AST or ALT > 10 x ULN
  - Total bilirubin > 5 x ULN
  - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade ≥ 3 motor neuropathy, regardless of causality
- Any dosing interruption lasting > 6 weeks with the following exceptions:
- Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued dosing of the particular drug given at the time of event

Subjects who permanently discontinue nivolumab or ipilimumab during Induction Period 1 may still be treated with the alternative agent in Induction Period 2, starting at Week 13, provided the criteria for resuming study treatment (Section 4.3.4.3) are met at that time.

Subjects in Cohort A who permanently discontinue ipilimumab during Induction Period 2 may still be treated with nivolumab in the Continuation Period, starting at Week 25, provided the criteria for resuming study treatment (Section 4.3.4.3) are met at that time and the criteria for discontinuation were not also met during prior nivolumab treatment during Induction Period 1.

Subjects who permanently discontinue nivolumab in Induction Period 1 (Cohort A) or Induction Period 2 (Cohort B) may not receive retreatment with nivolumab in the Continuation Period.

Subjects in the Continuation Phase will discontinue nivolumab after the completion of 2 years of study treatment (from the first dose of study treatment in Induction Period 1).

4.4 Blinding/Unblinding

Not applicable.

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

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

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

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

4.6.2 Return of Study Drug

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

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

4.7 Retained Samples for Bioavailability / Bioequivalence

Not applicable.

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209064)

Procedure	Screening Visit Within 28 days prior to Randomization	Notes
Eligibility Assessments		
Informed Consent	X	Section 2.3.
Inclusion/Exclusion Criteria	X	Section 3.3.
Medical History	X	Section 5.3.1.
ECOG Performance Status	X	Section 5.3.3.
Safety Assessments		
Physical Examination	X	Section 5.3.1.
Vital Signs & Oxygen Saturation	X	Section 5.3.2.
Height & Weight	X	Section 5.3.1.
ECG (12-lead)	X	Section 5.3.6. Obtained only for subjects who have met all eligibility criteria.
Assessment of Signs and Symptoms	X	Section 5.3.1. Within 14 days prior to Randomization.
Concomitant Medications	X	Section 3.4. Within 14 days prior to Randomization.
Laboratory Tests		
Chemistry & Hematology	X	Section 5.3.5. Within 14 days prior to Randomization.
Pregnancy Test (WOCBP Only)	X	Section 5.3.4.
Thryoid Function Testing	X	Section 5.3.5.1. Within 14 days prior to Randomization.
Hepatitis B & C	X	Section 5.3.5.2.
[redacted]		
[redacted]	[redacted]	[redacted]

Table 5.1-1: Screening Procedural Outline (CA209064)

Procedure	Screening Visit Within 28 days prior to Randomization	Notes
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Efficacy Procedures		
Tumor Assessment (CT/MRI)	X	Section 5.4. Chest, abdomen, pelvis, brain & all known sites of disease, within 28 days prior to Randomization.
Clinical Drug Supplies		
Enrollment (IVRS)	X	Section 4.2.

Table 5.1-2: Cohort A - Induction Period Procedural Outline

	Cohort A Induction Treatment (nivolumab followed by ipilimumab) +/- 3 Days										
	Induction Period 1						Induction Period 2				
Study Week	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W16**	**W19**	**W22**	**Notes**
Study Day	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D105**	**D127**	**D148**	
PROCEDURE											
Eligibility Assessments											
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	Section 5.3.3.
Safety Assessments											
Targeted Physical Examination	X						X				Section 5.3.1.
Weight	X	X	X	X	X	X	X	X	X	X	Section 5.3.1.
Vital Signs & Oxygen Saturation	X	X	X	X	X	X	X	X	X	X	Section 5.3.2.
[redacted]	[redacted]										[redacted]
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	Section 6.
Laboratory Tests											
Chemistry & Hematology	X	X	X	X	X	X	X	X	X	X	Section 5.3.5.
Pregnancy Test (WOCBP Only)	X			X			X	X	X	X	Section 5.3.4. Within 24 hours prior to initial administration of study drug.
Thyroid Function Testing				X			X	X	X	X	Section 5.3.5.1.
[redacted]	[redacted]										[redacted]

Table 5.1-2: Cohort A - Induction Period Procedural Outline

	Cohort A Induction Treatment (nivolumab followed by ipilimumab) +/- 3 Days										
	Induction Period 1						Induction Period 2				
Study Week	**W1**	**W3**	**W5**	**W7**	**W9**	**W11**	**W13**	**W16**	**W19**	**W22**	**Notes**
Study Day	**D1**	**D15**	**D29**	**D43**	**D57**	**D71**	**D85**	**D105**	**D127**	**D148**	
PROCEDURE											
Exploratory Biomarker Assessments											
Peripheral Blood Mononuclear Cell Assessments	X	X	X	X	X		X	X			Section 5.6.3.
Peripheral Blood Gene Expression Profiling	X	X	X				X	X			Section 5.6.4
[redacted]	[redacted]										[redacted]
Tumor Biopsy (fresh)							X				Section 5.6.1. Collected within 14 days prior to dosing.
Efficacy Procedures											
Tumor Assessment (CT/MRI)							X				Section 5.4. Chest, abdomen, pelvis, brain & all known sites of disease, to be performed prior to W13 dosing.
Clinical Drug Supplies											
Randomize (IVRS)	X										Section 4.2.
Nivolumab	X	X	X	X	X	X					Section 4.
Ipilimumab							X	X	X	X	Section 4.

Table 5.1-3: Cohort B - Induction Period Procedural Outline

	Cohort B Induction Treatment (ipilimumab followed by nivolumab) +/- 3 Days										
	Induction Period 1				Induction Period 2						
Study Week	**W1**	**W4**	**W7**	**W10**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**Notes**
Study Day	**D1**	**D22**	**D43**	**D64**	**D85**	**D99**	**D113**	**D127**	**D141**	**D155**	
PROCEDURE											
Eligibility Assessments											
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X	Section 5.3.3.
Safety Assessments											
Targeted Physical Examination	X				X						Section 5.3.1.
Weight	X	X	X	X	X	X	X	X	X	X	Section 5.3.1.
Vital Signs & Oxygen Saturation	X	X	X	X	X	X	X	X	X	X	Section 5.3.2.
[redacted]	[redacted]										[redacted]
Adverse Events Assessment	X	X	X	X	X	X	X	X	X	X	Section 6.
Laboratory Tests											
Chemistry & Hematology	X	X	X	X	X	X	X	X	X	X	Section 5.3.5.
Pregnancy Test (WOCBP Only)	X	X	X	X	X			X			Section 5.3.4. Within 24 hours prior to initial administration of study drug.
Thyroid Function Testing	X	X	X	X	X			X			Section 5.3.5.1.
[redacted]	[redacted]		[redacted]		[redacted]	[redacted]					[redacted]
Exploratory Biomarker Assessments											
Peripheral Blood Mononuclear Cell Assessments	X	X	X	X	X	X	X				Section 5.6.3.

Table 5.1-3: Cohort B - Induction Period Procedural Outline

	Cohort B Induction Treatment (ipilimumab followed by nivolumab) +/- 3 Days										
	Induction Period 1				Induction Period 2						
Study Week	**W1**	**W4**	**W7**	**W10**	**W13**	**W15**	**W17**	**W19**	**W21**	**W23**	**Notes**
Study Day	**D1**	**D22**	**D43**	**D64**	**D85**	**D99**	**D113**	**D127**	**D141**	**D155**	
PROCEDURE											
Peripheral Blood Gene Expression Profiling	**X**	**X**			**X**	**X**	**X**				Section 5.6.4.
[redacted]	[redacted]	[redacted]			[redacted]	[redacted]	[redacted]				[redacted]
Tumor Biopsy (fresh)					**X**						Section 5.6.1. Collected within 14 days prior to dosing.
Efficacy Procedures											
Tumor Assessment (CT/MRI)					**X**						Section 5.4. Chest, abdomen, pelvis, brain & all known sites of disease, to be performed prior to W13 dosing.
Clinical Drug Supplies											
Randomize (IVRS)	**X**										Section 4.2.
Nivolumab					**X**	**X**	**X**	**X**	**X**	**X**	Section 4.
Ipilimumab	**X**	**X**	**X**	**X**							Section 4.

Table 5.1-4: Continuation Period Procedural Outline (Cohort A & Cohort B)

Procedure	Continuation Period Starting at Week 25 Every 2 weeks +/- 3 days	Notes
Eligibility Assessments		
ECOG Performance Status	X	Section 5.3.3.
Safety Assessments		
Targeted Physical Examination	Week 25 & then as clinically indicated	Section 5.3.1.
Weight	X	Section 5.3.1.
Vital Signs & Oxygen Saturation	X	Section 5.3.2.
[redacted]	[redacted]	[redacted]
Adverse Events Assessment	X	Section 6.
Laboratory Tests		
Chemistry & Hematology	X	Section 5.3.5.
Pregnancy Test (WOCBP Only)	Week 25, then every 6 weeks	Section 5.3.4.
Thyroid Function Testing	Week 25, then every 6 weeks	Section 5.3.5.1.
[redacted]	[redacted]	[redacted]
Exploratory Biomarker Assessments		
Peripheral Blood Mononuclear Cell Assessments	Week 25, then every 12 weeks	Section 5.6.3.
Peripheral Blood Gene Expression Profiling	Week 25 only	Section 5.6.5
[redacted]	[redacted]	[redacted]
Tumor Biopsy (fresh)	At Progression	Section 5.6.1. Tumor biopsy required at time of progression.

Table 5.1-4: Continuation Period Procedural Outline (Cohort A & Cohort B)

Procedure	Continuation Period Starting at Week 25 Every 2 weeks +/- 3 days	Notes
Efficacy Procedures		
Tumor Assessment (CT/MRI)	Week 25, 33, 41 & 49. After Week 49: every 12 weeks	Section 5.4. To be performed prior to dosing. Scans may be done within 1 week of target week. At Week 25, Chest, abdomen, pelvis & brain required. At Week 33 & 41. Chest, abdomen, pelvis required. Brain scans should be done with tumor assessments, if there are known brain lesions. At Week 49, Chest, abdomen, pelvis and brain scan required. Beginning at Week 49, if there are no known brain lesions, brain scans required every 24 weeks.
Clinical Drug Supplies		
Nivolumab	X	Section 4. Maximum treatment duration is 2 years from first study treatment in Induction Period 1.

Table 5.1-5: Follow-Up & Survival Period (Cohort A & Cohort B)

Procedure	Initial Follow-Up Phase Follow-Up Visits 1 (X01) and 2 (X02)[a]	Survival (Y) Follow-Up Visits[b] Every 3 months	Notes
Safety Assessments			
Targeted Physical Examination	X		Section 5.3.1.
Vital Signs & Oxygen Saturation	X		Section 5.3.2.
Physical Measurements	X		Section 5.3.1
ECOG	X		Section 5.3.3.
Adverse Events Assessments	X	[X]	Section 6. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related adverse events until resolved, return to baseline, or deemed irreversible OR until lost to follow-up, withdrawal of study consent, or start of a subsequent anti-cancer therapy.
Chemistry & Hematology	X		Section 5.3.5.
Thyroid Function Testing	X		Section 5.3.5.1.
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]		[redacted]
Efficacy Assessments			
Tumor Assessment (CT/MRI)	Week 25, 33, 41 & 49. After Week 49: every 12 weeks	[X]	Section 5.4. To be performed prior to dosing. Scans may be done within 1 week of target week. At Week 25, Chest, abdomen, pelvis & brain required. At Week 33 & 41. Chest, abdomen, pelvis required. Brain scans should be done with tumor assessments, if there are known brain lesions. At Week 49, Chest, abdomen, pelvis and brain scan required. Beginning at Week 49, if there are no known brain lesions, brain scans required every 24 weeks.

Table 5.1-5: Follow-Up & Survival Period (Cohort A & Cohort B)

Procedure	Initial Follow-Up Phase Follow-Up Visits 1 (X01) and 2 (X02)[a]	Survival (Y) Follow-Up Visits[b] Every 3 months	Notes
Subject Status	X	X	Collection of survival information every 3 months until death, lost to follow-up, or withdrawal of study consent. May be performed by phone contact or office visit.

[a] X visits occur as follows: X01 = 30 days from last dose +/- 7 days. X02 = 70-84 days from X01.

[b] Y, survival visits occur every 3 months after X visits.

5.2 Study Materials

The following materials will be provided at study start:

- NCI CTCAE version 4.0
- BMS-936558 (nivolumab) Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy Binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of interactive voice response system, including enrollment/randomization 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

5.3 Safety Assessments

Subjects will be evaluated for safety if they have received any study drug (nivolumab or ipilimumab). Adverse events and laboratory values will be graded according to the NCI-CTCAE version 4.0. Additionally any occurrence of an SAE from the time of consent until 100 days after discontinuation of dosing and any SAE that is believed to be related to study drug or protocol-specified procedures after this time period will be documented.

5.3.1 Medical History, Physical Exam, Physical Measurements

At screening/baseline, a medical history will be obtained to capture relevant underlying conditions. The screening/baseline physical examination should include physical measurements (height, weight, ECOG Performance Status). These evaluations are to be performed at the screening visit and within 72 hours prior to the first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period and follow-up. See Table 5.1-1.

Weight is to be assessed prior to dosing at each dosing visit. Subsequent targeted physical examinations will be performed outlined in Table 5.1-1, Table 5.1-2 and Table 5.1-3 and as clinically indicated throughout the study. Any physical examination finding that qualifies as an AE or SAE must be documented on the appropriate CRF pages.

5.3.2 Vital Signs & Oxygen Saturation

Vital signs are to be assessed at each visit prior to dosing and include blood pressure (BP), heart rate, temperature, and oxygen saturation by pulse oximetry at rest and after exertion.

Vital signs are to be taken as per institutional standard of care prior to, during, and after dosing.

Oxygen saturation by pulse oximetry should be obtained prior to each new dose for subjects on both treatment cohorts and at any time a subject has any new or worsening respiratory symptoms. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary-related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 2 of the BMS-936558 (nivolumab) Investigator Brochure.

5.3.3 ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status will be evaluated and documented at Screening and at each dosing visit as outlined in Section 5.1. See Appendix 1 for description of ECOG status.

5.3.4 Pregnancy Testing

WOCBP are required to have pregnancy tests performed. WOCBP must exhibit a negative serum or urine pregnancy (minimum sensitivity 25 IU/L or equivalent units of HCG within 24 hours prior to the start of study drug. Pregnancy testing will be done locally and performed as outlined in, Table 5.1-1, Table 5.1-2,Table 5.1-3, Table 5.1-4.

5.3.5 Chemistry & Hematology Tests

Chemistry and Hematology tests will be performed as outlined in the tables in Section 5.1 and within 72 hours prior to dosing.

Chemistry tests are to include LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, calcium, magnesium, sodium, potassium, bicarbonate, chloride, lactate dehydrogenase (LDH), amylase, lipase and glucose.

Hematology tests are to include a CBC with differential.

Additional measures including non-study required laboratory tests should be performed as clinically indicated. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible. Management algorithms for suspected hepatotoxicity can be found in Appendix 4 of the BMS-936558 (nivolumab) Investigator Brochure and in Appendix 7 of the ipilimumab Investigator Brochure.

5.3.5.1 Thyroid Function Tests

Thyroid function tests will be performed as outlined in Section 5.1.

At Screening, thyroid function testing is to include TSH, free T3, and free T4. At subsequent timepoints, thyroid function testing consists of TSH only. However, if TSH is abnormal reflexive testing of free T3 and free T4 are to be performed. Management algorithms for suspected

endocrinopathy (including abnormal thyroid function) can be found in Appendix 5 of the BMS-936558 (nivolumab) investigator brochure and in Appendix 9 of the ipilimumab investigator brochure.

5.3.5.2 Hepatitis B & C Testing

Hepatitis B (HBV sAG) and Hepatitis C (HCV RNA) testing will be conducted during Screening.

5.3.6 Electrocardiogram (ECG)

All subjects who have met eligibility criteria are required to have a 12-lead ECG performed during Screening. If clinically indicated, additional ECGs may be obtained during the study.

5.3.7 Imaging Assessment for the Study

Not applicable.

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the tables in Section 5. Screening/baseline tumor assessments should be performed within 28 days prior to randomization utilizing CTs/MRI. In addition to chest, abdomen, pelvis, the brain and all known sites of disease should be assessed at screening/baseline. Subsequent assessments should include chest, abdomen, pelvis, and all known sites of disease and should use the same imaging method as was used at screening/baseline.

Change in tumor measurements and tumor responses will be assessed by the investigator using the RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria. For the secondary endpoint of response rate at Week 25, each subject's response at Week 25 will be evaluated in relation to baseline/screening tumor assessment independently of any other tumor assessments (including Week 13 or any unscheduled tumor assessments).

In the **Induction Period**, tumor assessments will be performed after the last dose in Induction Period 1 and prior to the first dose in Induction Period 2 (Week 13 +/- 1 week) and after the last dose in Induction Period 2 and prior to the first dose in the Continuation Period (Week 25 +/- 1 week). Brain scans are required at prior to dosing on Week 13 and Week 25.

In the **Continuation Period**, tumor assessments will be performed prior to dosing on Weeks 33 and 41 (+/- 1 week) and then every 12 weeks (prior to dosing) starting on Week 49 (+/- 1 week). If there are known brain lesions, brain scans should be done with the tumor assessments as indicated above. If there are no known brain lesions, brains scans are only required every 24 weeks beginning at Week 49.

In the **Follow-Up Period**, tumor assessments are to be performed on subjects that discontinue treatment for reasons other than progressive disease. Tumor assessments will be performed prior to dosing at Weeks 33 and 41 (+/- 1 week), then every 12 weeks (prior to dosing) starting on Week 49 (+/- 1 week) until progressive disease, withdrawal of study consent, subject is lost to follow-up, or start of a subsequent anti-cancer therapy. If there are known brain lesions, brain scans should be done with the tumor assessments as indicated above. If there are no known brain

lesions, brains scans are only required every 24 weeks beginning at Week 49 (brain scan is required at Week 49).

Tumor assessments **must not** be delayed until X01 or X02.

5.4.1 Assessment of Overall Tumor Burden and Measurable Disease

To serially evaluate tumor response to therapy, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable tumor lesion. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows in Sections 5.4.1.1, 5.4.1.2, and 5.4.1.3.

5.4.1.1 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 non-measurable)
- 20 mm by chest x-ray

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

5.4.1.2 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.

5.4.1.3 Special Consideration Regarding Lesion Measurability

Bone Lesions

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic Lesions

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

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same 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 loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

5.4.2 Specifications by Methods of Measurements

5.4.2.1 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.

5.4.2.2 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.

5.4.2.3 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.

5.4.2.4 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.

5.4.2.5 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.

5.4.2.6 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.

5.4.2.7 Endoscopy, Laparoscopy

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

5.4.2.8 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.

5.4.3 Baseline Documentation of "Target" and "Non-target Lesions"

5.4.3.1 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.

5.4.3.2 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.

5.4.3.3 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').

5.4.4 Tumor Response 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.

5.4.4.1 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.

5.4.4.2 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.

5.4.4.3 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'.

5.4.4.4 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.

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

5.4.4.5 When the Subject has Measurable Disease

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

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

5.4.5 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.

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

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 Scans

Verification of Response: Initial observations of response will be confirmed by repeat scans which should be performed no earlier than 4 weeks after the original observation to ensure that responses identified are not the result of measurement error. After an initial PR or CR is noted, the subsequent protocol-specified tumor assessment may serve as the confirmation. For the secondary endpoint of response rate at Week 25, any PR or CR at Week 25 may be confirmed by the scheduled tumor assessment at Week 33.

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.

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]			[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

5.7 Outcomes Research Assessments

Not applicable.

[redacted]

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

A S***erious Adverse Event (SAE)*** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

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

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).

6.1.1 Serious Adverse Event Collection and Reporting

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

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

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

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

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

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of **100** days following the last dose of study treatment.

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

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours and in accordance with SAE reporting procedures described in Section 6.1.1.

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

AND

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

AND

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

6.7 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiogram, x-ray filming, any other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

Not applicable.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

This trial is an estimation trial. Sample size in this study will be approximately 40 subjects per cohort and is not based on power considerations. Tables below provide the 95% confidence intervals computed from different observed rates. Those tables indicate what would be the reliability of the AE rate estimates for N=40 (Table 8.1-1) and N=35 (see Table 8.1-2) treated subjects. A threshold of 45% will be applied to the upper limit of the confidence interval as an informal guideline for high toxicity

Thirty-five subjects per cohort will be the minimum number of subjects receiving treatment in Induction Period 2. For that purpose, randomization will stay open until at least 40 subjects in each cohort have been treated with at least one dose of study treatment in Induction Period 1 and 35 subjects in each cohort have received at least one dose of study treatment in Induction Period 2. Assuming a drop-out rate during induction period 1 would be at most 12.5%, at least 35 subjects would be treated in induction period 2 if 40 subjects are to be randomized per cohort.

Table 8.1-1: Exact 95% CI width and upper bound for AE rates up to 40% when observed in 40 subjects

Nb Subj with Rel Gr3-5 A	Rate of Rel Gr3-5 AE	Exact 95% CI width	Upper limit Exact 95%CI
4	10%	21%	23.7%
8	20%	27%	35.6%
10	25%	29%	41.2%
11	27.5%	29%	43.9%
12	30%	30%	46.5%
13	32.5%	31%	49.1%
14	35%	31%	51.7%
16	40%	32%	57%

Table 8.1-2: Exact 95% CI width and upper bound for AE rates up to 40% when observed in 35 subjects.

Nb Subj with Rel Gr3-5 AE	Rate of Rel Gr3-5 AE	Exact 95% CI Width	Upper Limit Exact 95%CI
4	11.4%	23.5%	26.7%
7	20%	28.5%	36.9%
9	25.7%	30.8%	43.3%
10	28.6%	31.7%	46.3%
11	31.4%	32.4%	49.3%
14	40%	34%	57.9%

8.2 Populations for Analyses

All Enrolled Subjects: All subjects who signed an informed consent form and were registered into the IVRS.

All Randomized Subjects: All subjects who were randomized to any cohort in the study.

All Treated Subjects: All subjects who received at least one dose of study medication.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint

The primary endpoint of the study is the rate of treatment-related Grade 3-5 AEs during the Induction Period (Periods 1 and 2) in subjects receiving sequential induction treatment with either nivolumab followed by ipilimumab or ipilimumab followed by nivolumab.

The treatment-related Grade 3 - 5 AEs rate is defined as number of subjects who experienced at least 1 treatment related Grade3 - 5 adverse event (per NCI CTCAE v 4.0 criteria, any PT terms) with an onset date after or on first day of the Induction Period and not later than discontinuation date from the Induction Period, divided by number of treated subjects. AEs with an onset date after start of subsequent anti-cancer therapy, or start date of Continuation Period treatment will not be included.

- For subjects who discontinue Induction Period early and enter the Follow-Up Period, AEs that occur in Follow-Up, including those before Week 25, will not be included in the primary endpoint.
- For subjects who discontinue treatment before the end of Induction Period 1 or 2 but who are eligible to enter the next study period, AEs that occur before end of Induction Period 2 will be included in the primary endpoint, even if they occur after dosing ends while they are waiting to enter the next study period.

Primary and secondary endpoint analysis will be performed when at least 40 subjects per cohort have completed/discontinued Induction Period 1 and at least 35 subjects per cohort have completed/discontinued Induction Period 2 and all treated subjects with an objective response at Week 25 have been followed through study Week 33 in order to confirm disease response.

8.3.2 Secondary Endpoints

Secondary endpoints will be analyzed at the time of the primary endpoint analysis. Duration of response from Week 25 will be re-assessed at time of the OS update analysis.

8.3.2.1 Response Rate at Week 25

Response rate at Week 25 is defined as the number of subjects who have a complete response (CR) or partial response (PR) at Week 25, with confirmation at scheduled scan at Week 33, divided by the total number of randomized subjects. Note that the results of the tumor assessment at Week 13 will not be considered in the assessment of response rate at Week 25. This means, for example, that subjects with progressive disease at Week 13 are not precluded from having an assessment of CR or PR at Week 25 for this endpoint if the scan at Week 25 demonstrates such a response.

Duration of response (DOR) from Week 25 will also be assessed for subjects with confirmed response at Week 25 (see definition above). DOR is defined as the time between the Week 25 assessment date and the date of objectively documented disease progression (taking as reference

the smallest sum of diameters of target lesions beginning at Week 25) or death, whichever occurs first.

8.3.2.2 Progression Rates at Weeks 13 and 25

Progression rate at a specific timepoint is defined as the number of subjects who have Progressive Disease (PD) per RECIST 1.1 at that specific timepoint divided by the total number of randomized subjects.

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Primary Endpoint Analysis

Rate of treatment-related Grade 3-5 AEs during the induction period will be computed by treatment cohort using all treated subjects. Corresponding 95% CIs will be calculated using the Clopper-Pearson method.

As sensitivity analysis, rates and 95% CI will be also computed using the subset of subjects who received at least one dose of study treatment in Induction Period 2.

8.4.3 Efficacy Analyses

8.4.3.1 Response Rate at Week 25

Response rate at Week 25 will be computed by cohort using all randomized subjects. Response rate estimates and corresponding 95% CIs will be calculated using the Clopper-Pearson method.

As sensitivity analysis, response rates including only those subjects who were response evaluable at Week 25 (ie, those subjects with a tumor assessment at Week 25) will also be calculated.

8.4.3.2 DOR from Week 25

Duration of response from Week 25 will be assessed for subjects with confirmed response at Week 25. Median DOR estimate and corresponding 95% CIs will be provided for cohort using the Kaplan-Meier methodology

8.4.3.3 Progression Rates at Weeks 13 and 25

Progression rates at Week 13 and at Week 25 will be computed by cohort using all randomized subjects. Progression rate estimates and corresponding 95% CIs will be calculated using the Clopper-Pearson method.

[redacted]

8.4.4 Safety Analyses

Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by cohort. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term.

On-study lab parameters including hematology, chemistry, liver function, thyroid function and renal function will be summarized using worst grade per NCI CTCAE v 4.0 criteria.

Safety during Induction Period: see primary endpoint definition.

Safety during Induction Period 1: events considered will be those with an onset date during Induction Period 1. Rates of treatment related AEs will be computed using subjects treated in the induction Period 1. Treatment related AEs will be tabulated using worst CTC grades by system organ class and preferred term.

- For subjects who discontinue Induction Period 1 early and enter the Follow-Up Period, AEs that occur in Follow-Up will not be included.
- For subjects who discontinue treatment before the end of Induction Period 1 but who are eligible to enter the Induction period 2, AEs that occur before end of Induction Period 1 will be included, even if they occur after dosing ends while they are waiting to enter the next study period

- AEs with an onset date after start of subsequent anti-cancer therapy, or start date of Induction Period 2 treatment will not be included.

Safety during Induction Period 2: events considered will be those with an onset date during Induction Period 2. Rates of treatment related AEs will be computed using subjects treated in the induction Period 2. Treatment related AEs will be tabulated using worst CTC grades by system organ class and preferred term.

- For subjects who discontinue Induction Period 2 early and enter the Follow-Up Period, AEs that occur in Follow-Up will not be included.
- For subjects who discontinue treatment before the end of Induction Period 2 but who are eligible to enter Continuation Period, AEs that occur before end of Induction Period 2 will be included, even if they occur after dosing ends while they are waiting to enter the next study period
- AEs with an onset date after start of subsequent anti-cancer therapy, or start date of Continuation Period treatment will not be included. Worst CTC grades by system organ class and preferred term during Induction Period 2 will be reported.

The same analysis will be performed excluding AEs persisting from Induction Period 1 that are downgraded in Induction Period 2 compared to last grade observed in Induction Period 1.

Safety during Continuation Period: events considered will be those with an onset date during Continuation Period. Rates will be computed using subjects treated in the Continuation Period.

Overall safety on-treatment: events considered will be those with an onset date after (or on, if AE) first day of Induction Period treatment and up to 100 days after the last dose of study drug. Rates will be computed using all treated subjects.

[redacted]

[redacted]

8.4.7 Outcomes Research Analyses

Not Applicable.

8.4.8 Other Analyses

Not Applicable.

8.5 Interim Analyses

Not Applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

- IRB/IEC for review and approval/favorable opinion
- BMS
- Regulatory Authority(ies), if required by local regulations
- Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.

If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.

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

9.1.2 Monitoring

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

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by 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 investigational product (those supplied by BMS) is maintained at each study site where study drug and the following non-investigational product(s) are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label 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.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the paper or electronic SAE form and Pregnancy Surveillance form, respectively. Spaces may be left blank only in those circumstances permitted by study-specific CRF completion guidelines provided by 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, including any paper or electronic 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 considering the following criteria:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or their designee

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)
- Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as 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; 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.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
μg	microgram
β-HCG	beta-human chorionic gonadotrophin
ADA	Anti-Drug Antibody
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
$C1^-$	chloride
Ca^{++}	calcium
CBC	complete blood count
CFR	Code of Federal Regulations
CI	confidence interval
CL	Clearance
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CMV	cytomegalovirus
CNS	Central nervous system
CNS	Central Nervous System
CR	Complete Response
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
CT	Computed Tomography
CTA	Clinical Trial Agreement
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
D/C	discontinue
D	day

Term	Definition
DILI	Drug Induced Liver Injury
dL	deciliter
DLT	Dose limiting toxicity
DTIC	Dacarbazine
DNA	Deoxyribonucleic acid
DOR	Duration of response
DTIC	Dacarbazine
ECL	Electrochemiluminescent Immunoassay
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ESR	Expedited Safety Report
Fax	Facsimile
FDA	Food and Drug Administration
FFPE	Formalin-fixed paraffin-embedded
FISH	Fluorescent In Situ Hybridization
FSH	Follicle Stimulating Hormone
g	gram
G	Grade
GCP	Good clinical practice
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	Gastrointestinal
Gp	glycoprotein
h	hour
HBV	hepatitis B virus
HBVsAg	Hepatitis B surface antigen
HCG	Human chorionic gonadotropin
HCO_3^-	bicarbonate
HCV	hepatitis C virus
HCV RNA	Hepatitis C ribonucleic acid
HIPAA	Health information portability and accountability act
HIV	Human Immunodeficiency Virus
HR	heart rate

Term	Definition
HR	Hazard ratio
HRT	Hormone Replacement Therapy
IB	Investigator Brochure
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
IND	Investigational New Drug Exemption
Ipi	ipilimumab
irAE	Immune-related adverse event
IRB	Institutional Review Board
ISH	In situ hybridization
IU	International Unit
IV	Intravenous
IVRS	Interactive Voice Response System
K^+	potassium
K_3EDTA	potassium ethylenediaminetetraacetic acid
kg	kilogram
L	liter
LC	liquid chromatography
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
mAB	Monoclonal antibody
Mg	Milligram
Mg^{++}	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
MLR	Mixed lymphocyte reaction
Mm	Millimeters

Term	Definition
MRI	Magnetic resonance imaging
MTD	Maximum Tolerated Dose
N	number of subjects or observations
N/A	not applicable
Na^+	sodium
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse
NE	Not Evaluable
ng	nanogram
NIMP	Non-Investigational Medicinal Product
NK	Natural Killer
nM	nanometer
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral Blood Mononuclear Cell
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase chain reaction
PD	pharmacodynamics
PD	Progressive Disease
PD-1	Programmed Death-1
PD-L1	Programmed Death-Ligand 1
PET	Positron Emission Tomography
PFS	Progression free survival
PK	pharmacokinetic
PPK	Population pharmacokinetic
PR	Partial Response
Qty	Quantity
RBC	red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SD	standard deviation
SD	Stable Disease

Term	Definition
SNP	Single Nucleotide Polymorphism
SOP	Standard Operating Procedures
t	temperature
T	time
T.bilirubin	Total Bilirubin
TA	Tumor Assessment
TAO	Trial Access Online, the BMS implementation of an EDC capability
TCR	T-cell receptor
T-HALF	Half life
ULN	Upper Limit of Normal
US	United States
V	version
Vz	Volume of Distribution
W	Week
WBC	white blood cell
WHO	World Health Organization
Wk	Week
WOCBP	women of childbearing potential

APPENDIX 1 ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS	
1	Fully active, able to carry on all pre-disease performance without restriction
2	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

[redacted]

APPENDIX 2 GUIDANCE ON CONTRACEPTION

ACCEPTABLE METHODS FOR PROTOCOLS WITH A TERATOGENIC DRUG OR WHEN THERE IS INSUFFICIENT INFORMATION TO DETERMINE TERATOGENICITY

(CHOOSE ONE OF THE FOLLOWING 3 OPTIONS)[a]

OPTION 1: Any TWO of the following methods

- Hormonal methods of contraception[b, c, d]
- IUD[c, d, e]
- Vasectomy[d, f]
- Tubal Ligation[d]
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm[g]

OPTION 3: Male condom (with spermicide) and cervical cap[g]

[a] The theoretical failure rate for any of the options listed is considerably less than 1% per year

[b] Excludes progestin-only pills

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

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

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

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

[g] These 2 barrier methods together are acceptable for a teratogenic drug

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

In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of > 1%.

Women of childbearing potential (WOCBP) receiving BMS-936558 (nivolumab) will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for BMS-936558 (nivolumab) (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days after the last dose of BMS-936558 (nivolumab).