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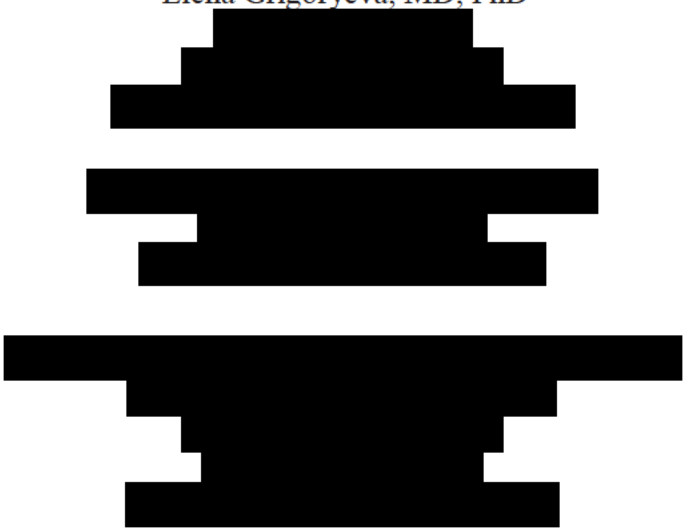
Clinical Protocol CA209401

Clinical Trial of Nivolumab (BMS-936558) Combined with Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma

CheckMate 401: **CHECK**point pathway and nivolu**MA**b clinical **T**rial **E**valuation 401

Revised Protocol 06

Study Director/Medical Monitor
Elena Grigoryeva, MD, PhD



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 06	31-Jul-2018	• Follow-up Phase shortened from 5 years after first dose to 2 years after first dose (or 2 years of treatment + 100 days of FU) • For patients discontinued in Part I, follow-up visits will be onsite only • Contraception wording changed based on updated Investigator's Brochure for nivolumab • Changes made to align with nivolumab program standards
Revised Protocol 05	19-Aug-2016	Incorporates Amendment 06
Amendment 06	19-Aug-2016	Incorporates the updated Pulmonary, Renal, and Skin Adverse Event Management Algorithms that were mistakenly not included in the Revised Protocol associated with Amendment 05.
Revised Protocol 04	03-Aug-2016	Incorporated Amendment 05 and Administrative Letter 02
Amendment 05	03-Aug-2016	• To revise the Management Algorithms to align with the new recommendations • To align with the nivolumab program standards, including changes to the duration of contraception use • To address minor inconsistencies in the protocol • To clarify that tumor assessments beyond Week 12 should be made according to the investigator's assessment.
Administrative Letter 02	28-Jun-2016	• Update the address of the Bristol-Myers Squibb Research and Development facility where the Medical Monitor is located • Clarify that the lettered numbering of the Inclusion Criteria was inadvertently re-numbered during the creation of the revised protocol associated with Amendment 04 • Clarify the Dose Delay Criteria for Grade 2 drug-related creatinine, aspartate aminotransferase, alanine aminotransferase, or total bilirubin • Clarify that tumor scans should also be completed for subjects who discontinue during the nivolumab and ipilimumab combination part (Part I) of the trial.
Revised Protocol 03	25-May-2016	Incorporated Amendment 04 and Administrative Letter 01
Amendment 04	25-May-2016	• Changes the nivolumab monotherapy dose in Part II to 240 mg flat dose for those subjects who enroll after the implementation of Amendment 04 • Decreases the infusion times of nivolumab and ipilimumab [redacted]
Administrative Letter 01	22-Mar-2016	• Align chemistry laboratory procedures throughout the screening, treatment, and follow-up phases and to remove the term serum from these procedures. • Align timing of receipt of testing results and dosing between the Time and Events Schedules and Section 5.3,

Document	Date of Issue	Summary of Change
		Safety Assessments. • Add footnotes to Table 5.1-2, On Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and Table 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy) to clarify that procedures for each time point should also be delayed if the dose is delayed • Clarify that investigators should follow the Management Algorithms in Appendix 1 for all grade adverse events rather than only Grades 3-4 in the Notes sections of Tables 5.1-2, On-Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy). • Remove dosing windows Tables 5.1-2, On-Study Assessments Part I: Cycles 1 through 4 (Nivolumab Plus Ipilimumab) and 5.1-3, On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy). • Add windows to Table 5.1-4, Follow Up Assessments for Subjects who Discontinue in Part I • Align the footnotes and Notes section related collection of adverse events in Tables 5.1-4, Follow Up Assessments for Subjects who Discontinue in Part I and 5.1-5, Follow-Up Assessments for Subjects who Discontinue in Part II to each other for consistency. • Remove the “Every 4 Week Column” from Table 5.1-5, Follow-Up Assessments for Subjects who Discontinue in Part II • Provide clarity on the timing of dosing when lipase test results are not available prior to dosing in Section 5.3, Safety Assessments. • Provide clarity on the timing of dosing in relation to receipt of test results as it differs for baseline assessments and on-treatment assessments.
Revised Protocol 02	05-Feb-2016	Incorporated Amendment 02
Amendment 02	05-Feb-2016	Removed Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome Exclusion Criterion
Revised Protocol 01	06-Jan-2016	Incorporated Amendment 01
Amendment 01	06-Jan-2016	• Changes Exclusion Criteria to known history of Human Immunodeficiency Virus (HIV) or Acquired Immunodeficiency Syndrome and removes HIV testing from the screening procedures. • Adds the definition of a Suspected Unexpected Serious Adverse Event • Requires local regulatory approval if applicable prior implementation of deviations or changes to the protocol.
Original Protocol	03-Jun-2015	Not applicable

SYNOPSIS

Clinical Protocol CA209401

Protocol Title: Clinical Trial of Nivolumab (BMS-936558) Combined with Ipilimumab Followed by Nivolumab Monotherapy as First-Line Therapy of Subjects with Histologically Confirmed Stage III (Unresectable) or Stage IV Melanoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s): Nivolumab 1 mg/kg IV over 30 minutes in combination with ipilimumab 3 mg/kg IV over 30 minutes every 3 weeks for 4 doses followed by nivolumab 3 mg/kg IV over 30 minutes every 2 weeks for up to 24 months from the first dose of regimen therapy. After implementation of Amendment 04, subjects will receive nivolumab 240 mg IV as a 30-minute infusion every 2 weeks in Part II.

Study Phase: 3b

Research Hypothesis: To characterize the incidence of high-grade (CTCAE v4.0 Grade 3 or higher), treatment-related, select adverse events of potentially immune-mediated etiology observed in a patient population reflective of routine, clinical practice and receiving nivolumab plus ipilimumab combination therapy in the first-line setting of advanced melanoma.

Objectives: The primary objective of this study is to determine the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity) of nivolumab plus ipilimumab combination regimen as first-line therapy for unresectable or metastatic melanoma.

The secondary objectives of this study are:

- To determine the incidence and to characterize the outcome (duration of serious adverse events [SAE] treatment, dose of immune-modulating agents [ie, steroids] used, time to event onset, and event resolution, and worst grade of event) of high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events of potentially immune-mediated etiology in subjects with unresectable or metastatic melanoma treated with nivolumab and ipilimumab combination regimen
- To estimate overall survival (OS) in all treated subjects
- To assess safety, tolerability, investigator-assessed objective response rate (ORR), progression-free survival (PFS), and OS in all subjects and in a subset of with Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0-1, ECOG PS 2, ocular and mucosal melanoma, and brain metastasis

Study Design: The study will include subjects who will receive first-line therapy for advanced disease with histologically-confirmed unresectable stage III or stage IV melanoma, ages 18 or older. Subjects will be treated with nivolumab 1 mg/kg IV as a 30-minute infusion combined with ipilimumab 3 mg/kg IV as a 30-minute infusion every 3 weeks for 4 doses (Part I) and then nivolumab 3 mg/kg IV every 2 weeks (Part II) until progression, unacceptable toxicity, or a maximum of 24 months from first combination dose (Part I and Part II), whichever comes first. At sites who begin enrolling subjects after the implementation of Amendment 04, subjects will receive nivolumab 240 mg IV as a 30-minute infusion every 2 weeks in Part II. Approximately 768 subjects will be considered for enrollment, and approximately 615 will be treated.

This study will consist of 3 phases: Screening, Treatment, and Follow-up.

The Screening Phase begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subjects are enrolled using the Interactive Voice Response System (IVRS).

[redacted]

The Treatment Phase begins with the vial assignment call to the IVRS. A negative pregnancy test should be documented within 24 hours prior to the start of investigational product. An extension of up to 72 hours prior to the first dose of nivolumab and ipilimumab is allowed in situations where results cannot be obtained within the standard 24 hour window.

For Part I, nivolumab and ipilimumab are administered every 3 weeks for 4 doses. For Part II, nivolumab monotherapy is administered every 2 weeks for up to 24 months from the first combination dose (Part I and II). Subjects may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the Treatment Phase.

An initial tumor assessment is to be completed at Week 12 (±5 days) after the first treatment dose. Further tumor assessments are recommended to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks until documented tumor progression.

The Follow-up Phase begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy):

- Subjects who discontinue therapy in Part I are recommended to be followed by direct contact (office visit) every 4 weeks for up to 100 days after the last dose of regimen therapy. After completion of the onsite follow-up visits (for up to 100 days), subjects will be followed every 24 weeks ± 2 weeks for survival either by direct visit or via telephone contact. OS will be followed from the start of therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete or discontinue therapy in Part II, subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug. After completion of the first 2 follow-up visits, subjects will be followed every 24 weeks ± 2 weeks for survival either by direct contact or via telephone contact. OS will be followed from the start of therapy up to 2 years (+ 100 days following the last dose of study treatment), or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete therapy in Part II (2 years of treatment), subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug.

Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments according to the local standard of care for up to 2 years. All adverse events (adverse events) will be documented for a minimum of 100 days after last dose.

Study Population	Treatment	Duration of Treatment
• Unresectable or metastatic melanoma • First-line subjects for advanced disease	**Part I:** nivolumab 1 mg/kg IV + ipilimumab 3 mg/kg IV every 3 weeks X 4	**Part I:** treat for 12 weeks (4 doses)
	Part II: nivolumab 3 mg/kg or 240 mg[a] IV every 2 weeks until progression or a maximum of 24 months from the first combination dose (Part I and Part II) whichever comes first.	**Part II:** treat for a maximum of 24 months[b] from first combination dose (Part I and Part II) until progression[c] or unacceptable toxicity.

Part I (3 months) + **Part II** (up to 21 months) = maximum of 24 months

[a] Sites who begin enrollment after the implementation of Amendment 04 will administer 240 mg IV instead of 3 mg/kg.

[b] In case of an on-hold period during therapy, subjects may be treated for more than 24 months but for a maximum of 50 cycles.

[c] Subjects may be treated beyond progression under protocol-defined circumstances.

Study Population:

Key Inclusion Criteria:

a) Subjects with histologically-confirmed unresectable stage III or stage IV melanoma as per AJCC 2010 staging system, including mucosal and ocular melanoma, regardless of BRAF mutation status

b) Subjects are included if they are newly diagnosed with advanced/metastatic disease and have not received prior systemic treatment for their advanced disease.

NOTE: Prior adjuvant or neoadjuvant melanoma therapy (including anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, such as anti-CD-137) is permitted if the therapy was used in the adjuvant or neoadjuvant setting but not in the metastatic setting. These drugs must be discontinued 6 months prior to study entry. All AEs related to prior adjuvant or neoadjuvant therapy must have either returned to baseline, and eligible patients must not have experienced severe or life-threatening irAEs except those that are unlikely to reoccur with standard countermeasures (eg, hormone replacement after adrenal crisis).

c) Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 2 weeks after treatment is complete and within 6 weeks prior to first dose of study drug administration. (If MRI is contraindicated, CT scan is acceptable). There must also be no requirement for high doses of systemic corticosteroids that could result in immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

i) Subjects are eligible if they have previously untreated brain metastases and are neurologically asymptomatic (This criterion is restricted to the investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen):

(1) No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or

other systemic therapy.

(2) Subjects must be free of neurologic signs and symptoms related to metastatic brain lesions and must not have received systemic corticosteroid therapy in the 14 days prior to beginning protocol therapy.

ii) If patients had been previously treated and then developed asymptomatic progression (This criterion with details below is restricted to the investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen)

(1) Prior stereotactic radiotherapy (SRT) and prior excision of up to 3 melanoma brain metastases is permitted if there has been complete recovery, with no neurologic sequelae.

(2) Growth or change in a lesion previously irradiated will not be considered measurable. Regrowth in cavity of previously excised lesion will not be considered measurable.

(3) Any prior surgery or radiotherapy must have occurred at least 6 weeks before the start of dosing for this study.

d) ECOG PS 0-1

e) ECOG PS of 2 (This criterion is restricted to investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen)

f) Tissue tumor (archival or recent acquisition) must be available (block or a minimum of 10 unstained slides of FFPE tissue) for correlative studies

Key Exclusion Criteria

a) Leptomenigeal metastases

b) As of Amendment 04, this criterion is no longer applicable

c) Subjects previously treated with SRT > 3 lesions in the brain

d) Brain lesion > 3 cm

e) History of carcinomatous meningitis (lumbar puncture is not required)

f) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

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

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

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

Study Drug for BMS-936558		
Medication	**Potency**	**IP/Non-IP**
Nivolumab	100 mg (10 mg/mL) Or 40 mg (10 mg/mL)	IP
Ipilimumab	200 mg (5 mg/mL)	IP

Study Assessments: The following safety assessments should be monitored every cycle, except where noted, starting with dosing until approximately 100 days following the discontinuation from study therapy, providing AEs have resolved:

- AEs continuously throughout the study
- Physical examination and physical measurements including weight and ECOG performance status
- Complete blood counts (CBCs) with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count. Laboratory tests should be completed and reviewed within 72 hours prior to dosing.
- Chemistry tests (BUN or serum urea level, creatinine, sodium, potassium, calcium, phosphate, chloride, magnesium, glucose, amylase, lipase, and LDH). Laboratory tests should be completed with 72 hours and reviewed prior to dosing. If sites are unable to obtain lipase results prior to dosing, dosing may still occur provided all other safety laboratory results including amylase are available and reviewed by the investigator prior to dosing.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin. Laboratory tests should be completed within 72 hours and reviewed prior to dosing.
- Thyroid function testing, including TSH (reflex to free T3 and free T4 if abnormal results), to be checked every 6 weeks. Laboratory tests should be completed within 72 hours and reviewed prior to dosing.
- Concomitant medications will be collected at the screening visit, throughout the Treatment Phase, and Follow-up Phase.

Subjects will also receive a weekly phone call to report AEs on the weeks without required study visits. After completion of the visits up to 100 days after the last dose of study drug, OS will be followed by direct contact (office visits) or via telephone contact, until death, withdrawal of study consent, or lost to follow-up for up to 2 years from the first dose of study treatment (+ 100 days following the last dose of study treatment). OS is defined as the time between the start of treatment and the date of death due to any cause.

Efficacy assessments include an initial tumor assessment at Week 12 (± 5 days) after first combination dose. Further tumor assessments to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks. Quality-of-life data will be measured using the EORTC QLQ-C30 every 2 cycles (6 weeks) during ipilimumab and nivolumab combination regimen treatment and then every 4 cycles (8 weeks) while receiving nivolumab monotherapy starting with Cycle 5.

Statistical Considerations:

Sample Size: Of 768 subjects who will be screened to receive first-line therapy for advanced disease with histologically confirmed stage III (unresectable) or stage IV melanoma, approximately 615 subjects will be treated with nivolumab and ipilimumab regimen. This sample size is based on the primary objective of the study: determining the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology in subjects receiving first-line therapy for advanced disease. The sample size will allow for estimating an incidence of about 50% with a 95% confidence interval (CI) of (46.06%, 54.11%) under 308 subjects with events among 615 treated subjects.

Endpoints: The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity).

The secondary endpoints are:

- Incidence of all high-grade (Grades 3-5), select adverse events
- Median time to onset and median time to resolution (Grades 3-4) of select adverse events

- Resolution of an AE is a subject experiencing complete resolution or improvement to the baseline grade for the AE
- OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- Safety and tolerability will be measured by the incidence of all AEs, treatment-related AEs, serious AEs, deaths, laboratory abnormalities, and select AEs such as pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity.
- The ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of all treated subjects. BOR is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression by the investigator or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.
- Investigator-assessed PFS is defined as radiological evidence of progression, significant clinical symptomatic progression, or the need to introduce a non-study drug therapy.

Analyses: Descriptive statistics will be presented for each of the endpoints. The analysis of primary, secondary, and exploratory endpoints will be reported for the full safety analysis set (all treated subjects) and by subgroups based on ECOG PS, brain metastasis, ocular and mucosal melanoma, and investigator experience in treating with the nivolumab plus ipilimumab combination regimen. The number and percentage of subjects who report high-grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology will be summarized for all treated subjects overall. High-grade (Grade 3-5), treatment-related select adverse events will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. The number and percentage of subjects who report high-grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology will be summarized for all treated subjects overall and by subgroup. High-grade (Grade 3-5), treatment-related, select adverse events will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. Time to onset and resolution of the events, dose of immune modulating medications subjects received for the events, and the event by grade will also be tabulated for all treated subjects and by subgroups. Cumulative doses of immune-modulating agents will be summarized and reported.

Time to onset and resolution of the events, dose of immune modulating medications subjects received for the events, and the event by grade will also be tabulated for all treated subjects and by subgroup. All safety data will be listed and tabulated for all treated subjects. All AEs, treatment-related AEs, serious AEs, deaths, and select AEs such as pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity will be summarized by system organ class and preferred term, and coded according to the most current version of MedDRA.

OS will be summarized by Kaplan-Meier method for all treated subjects and by cohort. Median values of OS, along with 2-sided 95% CI using Brookmeyer and Crowley method, will be calculated.

The investigator-assessed ORR will be summarized by binomial response rates and their corresponding 2-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects and by subgroup. The DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier method. Median values of DOR, along with 2-sided 95% CI using Brookmeyer and Crowley method, will also be calculated. The abovementioned OS, investigator-assessed ORR, and safety and tolerability will be conducted specifically for subjects with PS 2, ocular or mucosal melanoma.

TABLE OF CONTENTS

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1 INTRODUCTION AND STUDY RATIONALE

[redacted]

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objectives

The primary objective of this study is to determine the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity) of nivolumab plus ipilimumab combination regimen as first-line therapy for unresectable or metastatic melanoma.

1.3.2 Secondary Objectives

The secondary objectives of this study are:

- To determine the incidence and to characterize the outcome (duration of serious adverse event [SAE] treatment, dose of immune-modulating agents [ie, steroids] used, time to event onset, and event resolution, and worst grade of event) of high-grade (CTCAE v4.0 Grade 3 or higher), select adverse events of potentially immune-mediated etiology in subjects with unresectable or metastatic melanoma treated with nivolumab and ipilimumab combination regimen
- To estimate OS in all treated subjects
- To assess safety, tolerability, investigator-assessed objective response rate (ORR), PFS, and OS in all subjects and in a subset of with ECOG PS 0-1, ECOG PS 2, ocular and mucosal melanoma, and brain metastases.

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

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

Investigators must:

Provide a copy of the consent form and written information about the study in the language in which the subject is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

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

Obtain an informed consent signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion.

Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.

If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the subject subsequently becomes capable of making and communicating his or her informed consent during the study, consent must additionally be obtained from the subject.

Revise the informed consent whenever important new information becomes available that is relevant to the subject's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the subject's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the subject's willingness to continue participation in the study. This communication should be documented.

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

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

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her

understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

The study will include subjects who will receive first-line therapy for advanced disease with histologically-confirmed unresectable stage III or stage IV melanoma, ages 18 or older. Subjects will be treated with nivolumab 1 mg/kg IV as a 30-minute infusion combined with ipilimumab 3 mg/kg IV as a 30-minute infusion every 3 weeks for 4 doses (Part I) and then nivolumab 3 mg/kg IV every 2 weeks (Part II) until progression, unacceptable toxicity, or a maximum of 24 months from the first combination dose (Part I and Part II), whichever comes first. Subjects may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the Treatment Phase. At sites who begin enrolling subjects after the implementation of Amendment 04, subjects will receive nivolumab 240 mg IV as a 30-minute infusion every 2 weeks in Part II. Approximately 768 subjects will be considered for enrollment, and approximately 615 will be treated.

This study will assess the safety and efficacy of nivolumab combined with ipilimumab in adults (≥ 18 years) with stage III (unresectable) or stage IV melanoma, as per the American Joint Committee on Cancer (AJCC) staging system. Subjects must not have received prior therapy for the treatment for metastatic disease.

This study will consist of 3 phases: Screening, Treatment, and Follow-up.

The Screening Phase begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF). Subjects are enrolled using the Interactive Voice Response System (IVRS) (Table 5.1-1).

Per Amendment 04 (25-May-2016): Tumor tissue (archival or recent acquisition) must be available for assessment of tumor PD-L1 expression by immunohistochemical and other tumor tissue biomarker studies. Subjects must consent to allow the acquisition of formalin-fixed paraffin-embedded (FFPE) material (block or 10 unstained slides) by study personnel for performance of correlative tissue studies.

The Treatment Phase begins with the vial assignment call to the IVRS. A negative pregnancy test should be documented within 24 hours prior to the start of investigational product. An extension of up to 72 hours prior to the first dose of nivolumab and ipilimumab is allowed in situations where pregnancy test results cannot be obtained within the standard 24 hour window.

For Part I, nivolumab and ipilimumab are administered every 3 weeks for 4 doses (Table 5.1-2). If subjects discontinue therapy during Part I, nivolumab monotherapy can be continued as

described in Section 4.5.5. **For Part II,** nivolumab monotherapy is administered every 2 weeks (Table 5.1-3) until 24 months after the first combination dose (Part I and II). Subjects may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the Treatment Phase.

Windows for dosing of both Part I and Part II are discussed in Section 4.5.

An initial tumor assessment is to be completed at Week 12 (± 5 days) after the first treatment dose. Further tumor assessments are recommended to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks until documented tumor progression.

Subjects treated with the study drugs will be permitted to continue treatment beyond initial PD as assessed by the investigator's clinical judgment and local standards of care as long as they meet the criteria specified in Section 4.5.8.

The Treatment Phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Sections 3.5 and 4.5.6.

The Follow-up Phase begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy) (Table 5.1-4 and Table 5.1-5):

- Subjects who discontinue therapy in Part I are recommended to be followed by direct contact (office visit) every 4 weeks for up to 100 days after the last dose of combination regimen therapy. After completion of the onsite follow-up visits (for up to 100 days), subjects will be followed every 24 weeks ± 2 weeks for survival either by direct visit or via telephone contact. OS will be followed from the start of therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete or discontinue therapy in Part II, subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug. After completion of the first 2 follow-up visits, subjects will be followed every 24 weeks ± 2 weeks for survival either by phone contact or direct contact. OS will be followed in accordance with Table 5.1-4 and Table 5.1-5 from the start of therapy up to 2 years (+ 100 days following the last dose of study treatment), or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete therapy in Part II (2 years of treatment), subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug.

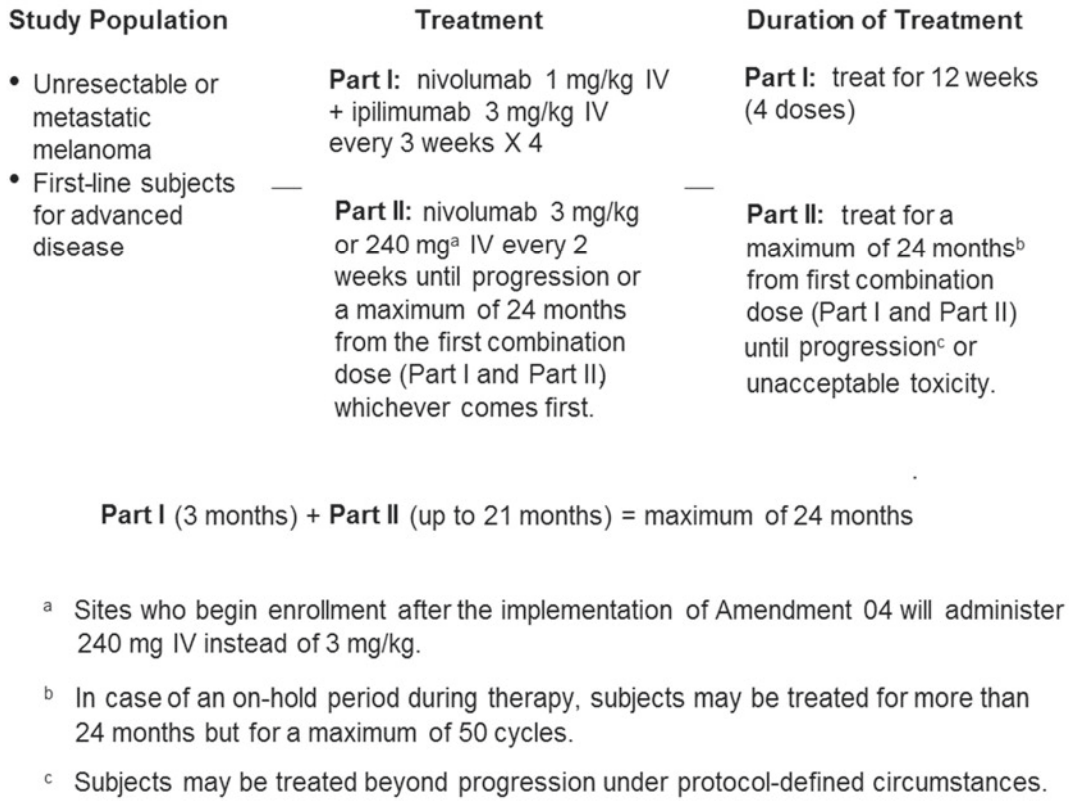
Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments according to the local standards of care and in accordance with Table 5.1-4 and Table 5.1-5.

Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline, are deemed irreversible, lost to follow up, or withdrawal of study consent. All AEs will

be documented for a minimum of 100 days after last dose. Additional details regarding the follow up are discussed in Section 5.3, Table 5.1-4, and Table 5.1-5.

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

Figure 3.1-1: Study Design Schematic



The start of the trial is defined as the first patient's first study visit. End of trial is defined as the last patient's last study visit. Study completion is defined as the final date on which data for the primary endpoint was or is expected to be collected, if this is not the same.

Enrollment of new subjects into the study will stop at the time of marketing authorization approval. In certain countries where nivolumab plus ipilimumab combination regimen may not be immediately available upon marketing authorization and subject to country specific amendments, enrollment may remain open for a maximum of 1 year after marketing authorization is granted.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive BMS supplied study drug **for the maximum treatment duration specified in Section 3.1**. Study drug will be provided via an extension of the study, a rollover study requiring

approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS.

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

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

a) Subjects must have signed and dated an IRB/IEC-approved written informed consent form in accordance with regulatory and local 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, and laboratory tests, including completion of quality of life questionnaires and other requirements of the study.

2. Target Population

a) Subjects with histologically-confirmed unresectable stage III or stage IV melanoma as per AJCC 2010 staging system, including mucosal and ocular melanoma, regardless of BRAF mutation status. [73]

b) Subjects are included if they are newly diagnosed with advanced/metastatic disease and have not received prior systemic treatment for their advanced disease.

NOTE: Prior adjuvant or neoadjuvant melanoma therapy (including anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-PD-L2, or any other antibody or drug specifically targeting T-cell costimulation or checkpoint pathways, such as anti-CD-137) is permitted if the therapy was used in the adjuvant or neoadjuvant setting but not in the metastatic setting. These drugs must be discontinued 6 months prior to study entry. All AEs related to prior adjuvant or neoadjuvant therapy must have returned to baseline, and eligible patients must not have experienced severe or life-threatening irAEs except those that are unlikely to reoccur with standard countermeasures (eg, hormone replacement after adrenal crisis).

c) Although lesions measured by physical exam (calipers) can be considered measurable, at least 1 target lesion must be measurable by CT or MRI per RECIST 1.1[74]

d) Prior radiotherapy or radiosurgery must have been completed at least 2 weeks prior to the first dose of study drug

e) Subjects with brain metastases are eligible if these metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 2 weeks after treatment is complete and within 6 weeks prior to first dose of study drug administration. (If MRI is contraindicated, CT scan is acceptable.) There must also be no requirement for high doses of systemic corticosteroids that could result in

immunosuppression (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

i. Subjects are eligible if they have previously untreated brain metastases and are neurologically asymptomatic (This criterion is restricted to investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen)
    1) No clinical requirement for local intervention (surgery, radiosurgery, corticosteroid therapy) or other systemic therapy.
    2) Subjects must be free of neurologic signs and symptoms related to metastatic brain lesions and must not have received systemic corticosteroid therapy in the 14 days prior to beginning protocol therapy.

ii. If subjects had been previously treated, and then developed asymptomatic progression (This criterion with details below is restricted to investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen)
    1) Prior stereotactic radiotherapy (SRT) and prior excision of up to 3 melanoma brain metastases is permitted if there has been complete recovery, with no neurologic sequelae.
    2) Growth or change in a lesion previously irradiated will not be considered measurable. Regrowth in cavity of previously excised lesion will not be considered measurable.
    3) Any prior surgery or radiotherapy must have occurred at least 6 weeks before the start of dosing for this study

f) Screening laboratory values must meet the following criteria and should be obtained prior to commencement of treatment:

i. White blood counts (WBC) ≥ 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 × upper limit of normal [ULN] or creatinine clearance (CrCL) > 40 mL/minute (using Cockcroft/Gault formula)
    i) Female CrCl= [(140- age in years) × weight in kg X 0.85) ÷ (72 × serum creatinine in mg/dL)]
    ii) Male CrCl= [(140- age in years) × weight in kg × 1.00) ÷ (72 × serum creatinine in mg/dL)]

vi. AST ≤ 3 × ULN

vii. ALT ≤ 3 × ULN

viii. Total bilirubin ≤ 1.5 × ULN (except subjects with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL)

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

h) ECOG PS 0-1

i) ECOG PS of 2 (This criterion is restricted to investigators who have treated at least 3 patients with nivolumab plus ipilimumab combination regimen)

j) Tissue tumor (archival or recent acquisition) must be available (block or a minimum of 10 unstained slides of FFPE tissue) for correlative studies

3. Age and Reproductive Status

a) Men and women, aged ≥18 years

b) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drugs plus 5 half-lives plus 30 days (duration of ovulatory cycle). Because the half-life of nivolumab is longer than that of ipilimumab, subjects must agree to continue contraception for a total of 5 months post-treatment completion.

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with nivolumab plus 5 half-lives of the study drug plus 90 days (duration of sperm turnover). Because the half-life of nivolumab is longer than that of ipilimumab, subjects must agree to continue contraception for a total of 7 months post-treatment completion.

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

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly. Local laws and regulations may require use of alternative and/or additional contraception methods.

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as 5 months after the end of study treatment.

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, implantable, or injectable)
- Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants, and intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomized partner

NOTE: A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- Intrauterine devices (IUDs)
- Sexual abstinence

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 5.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participants chooses to forego complete abstinence.

UNACCEPTABLE METHODS OF CONTRACEPTION

- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge with spermicide
- Male or female condom with or without spermicide. Male and female condoms must not be used simultaneously.
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILD BEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the investigator.
- Male participants are required to use a condom for study duration and until end of relevant systemic exposure defined as 7 months after the end of study treatment.

- Female partners of males participating in the study to consider use of effective methods of contraception until the end of relevant systemic exposure, defined as 7 months after the end of treatment in the male participant.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and until 7 months after the end of study treatment.
- Refrain from donating sperm for the duration of the study treatment and until 7 months after the end of study treatment.

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

a) Leptomeningeal metastases
b) Subjects previously treated with SRT > 3 lesions in the brain
c) Brain lesion > 3 cm
d) History of carcinomatous meningitis (lumbar puncture not required)

2. Medical History and Concurrent Diseases

a) As of Amendment 04, this criterion is not applicable
b) Subjects who are expected to require any form of systemic antineoplastic therapy while receiving study drug(s)
c) Subjects with active, known, or suspected autoimmune disease. Subjects with Type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
d) Subjects with previous malignancies (except non-melanoma skin cancer and the following in situ cancers: bladder, gastric, colon, endometrial, cervical/dysplasia, or breast) are excluded unless a complete remission was achieved at least 1 year prior to study entry AND no additional therapy is required during the study period
e) Subjects with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement steroid doses > 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
f) 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 subject to receive protocol therapy
g) All toxicities attributed to prior anti-cancer therapy other than alopecia, fatigue, or peripheral neuropathy must have resolved to Grade 1 (NCI CTCAE version 4) or baseline before administration of study drug
h) As of Amendment 02, this criterion is no longer applicable.

3. **Physical and Laboratory Test Findings**
   a) Any positive test result for hepatitis B virus or hepatitis C virus during screening indicating acute or chronic infection
   b) As of Amendment 01, this criterion is no longer applicable.
4. **Allergies and Adverse Drug Reaction**
   a) History of severe hypersensitivity reactions to other monoclonal antibodies
   b) History of allergy or intolerance (unacceptable AEs) to study drug components or Polysorbate-80-containing infusions
5. **Sex and Reproductive Status**
   a) WOCBP who are pregnant or breastfeeding
   b) Women with a positive pregnancy test at enrollment or prior to administration of study medication
6. **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

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

Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period in order to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. The duration of the washout period below are suggested guidelines and the investigators should use their judgement in checking serum FSH levels. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal:

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

[redacted]

3.5 Discontinuation of Subjects following any Treatment with Study Drug

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (Section 4.5.6)

All subjects who discontinue investigational product should comply with protocol-specified follow-up 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).

Subjects who request to discontinue study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures (Table 5.1-4 and Table 5.1-5). 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.

In the case of pregnancy, the investigator must immediately notify the BMS Medical Monitor/designee of this event. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study drug, a discussion between the investigator and the BMS Medical Monitor/designee must occur.

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

3.6 Post Study Drug Study Follow up

BMS may request that survival data be collected on all treated participants outside of the protocol-defined window (see Section 5.1, Flow Chart/Time and Events Schedule). At the time of this request, each participant will be contacted to determine their survival status unless the participant has withdrawn consent for all contacts or is lost to follow-up.

In this study, safety is a key endpoint of the study. Post-study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study. The Follow-up Phase is described in Table 5.1-4 and Table 5.1-5.

3.6.1 Withdrawal of Consent

Subjects who request to discontinue study drug will remain in the study and must continue to be followed for protocol specified follow-up procedures. The only exception to this is when a subject specifically withdraws consent for any further contact with him/her or persons previously authorized by subject to provide this information. Subjects should notify the investigator of the decision to withdraw consent from future follow-up **in writing**, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is from further treatment with study drug only or also from study procedures and/or post treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-

retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

- nivolumab
- ipilimumab

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solution used as diluent solutions (0.9% sodium chloride injection, 5% dextrose injection) should also be sourced by investigative sites if available and permitted by local regulations.

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

- nivolumab
- ipilimumab

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

- 0.9% sodium chloride injection solution
- 5% dextrose injection solutions (diluents).

Table 4-1: Study Drugs for CA209401: Part I

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL)	10 mL per vial/ Open-label	10 or 5 vials per carton/ Open-label	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	Store at 2°-8°C (36°-46°F). Protect from light and freezing.
Ipilimumab (Yervoy) Solution for Injection	200 mg (5 mg/mL)	40 mL per vial/Open-label	One single use vial per carton/open-label	Clear, colorless to pale yellow liquid. May contain particles	Store at 2°-8°C (36°-46° F). Protect from light and freezing.

Table 4-2: Study Drugs for CA209401: Part II

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
Nivolumab Solution for Injection	100 mg (10 mg/mL) Or 40 mg (10 mg/mL)	10 mL per vial/ Open-label Or 4 mL per vial/Open-label	10 or 5 vials per carton/ Open-label Or 240 mg flat dose kits (2-100 mg vials and 1-40 mg vial)	Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.	Store at 2°-8°C (36°-46°F). Protect from light and freezing.

4.1 Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as 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.

4.2 Non-investigational Product

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

4.3 Storage and Dispensing

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

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

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

4.3.1 Part I Study Drug Administration (Combination)

Subjects should receive nivolumab at a dose of 1 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

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

The second infusion in the combination cohort will always be ipilimumab and will start at least 30 minutes after the infusion line has been flushed, filters changed, and patient has been observed to ensure no infusion reaction has occurred. Subjects should receive ipilimumab at a dose of 3 mg/kg as a 30-minute IV infusion, on Day 1 of each treatment cycle every 3 weeks for 4 doses or until progression, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first.

As of Amendment 04, all subjects will transition to the 30-minute infusion time for both nivolumab and ipilimumab.

4.3.2 Part II Study Drug Administration (Monotherapy)

Subjects should receive nivolumab at a dose of 3 mg/kg as a 30-minute IV infusion on Day 1 of each treatment cycle every 2 weeks until progression, unacceptable toxicity, or a maximum of 24 months from the first dose of the combination regimen (Part I and II), whichever comes first. Subjects may be treated for more than 24 months for a maximum of 50 cycles in case an on-hold period occurs during the Treatment Phase.

At all sites who begin to enroll subjects after the implementation of Amendment 04, nivolumab will be administered at a dose of 240 mg IV every 2 weeks as a 30-minute infusion until progression, unacceptable toxicity, a maximum of 24 months from the first dose of the combination regimen (Part I and II), or the study ends, whichever comes first. Subjects may be treated for more than 24 months but for a maximum of 50 cycles in case an on-hold period occurs during the Treatment Phase.

4.4 Method of Assigning Subject Identification

After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. 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

4.5 Selection and Timing of Dose for Each Subject

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

Table 4.5-1: Dosing Schedule for Part I

Every 3 Week Dosing One Cycle = 3 weeks			
Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4**
1 mg/kg nivolumab/ 3 mg/kg ipilimumab	1 mg/kg nivolumab/ 3 mg/kg ipilimumab	1 mg/kg nivolumab/ 3 mg/kg ipilimumab	1 mg/kg nivolumab/ 3 mg/kg ipilimumab

Table 4.5-2: Dosing Schedule for Part II			
Every 2 Week Dosing[a] 1 Cycle = 2 weeks			
Cycle 5[b]	**Cycle 6**	**Cycle 7**	**Cycle 8 to Cycle 50 (last possible Cycle)**
3 mg/kg nivolumab Or 240 mg	3 mg/kg nivolumab Or 240 mg	3 mg/kg nivolumab Or 240 mg	3 mg/kg nivolumab Or 240 mg

[a] At sites who begin enrollment after the implementation of Amendment 04, nivolumab will be administered at a dose of 240 mg IV instead of 3 mg/kg.

[b] Cycle 5 is to occur 3 weeks after Cycle 4.

Ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab 1 mg/kg will be infused over 30 minutes. After a 30-minute break between infusions, ipilimumab (3 mg/kg) will be infused over 30 minutes.

The dosing calculations should be based on body weight for subjects receiving nivolumab 1 mg/kg and ipilimumab in Part I and 3 mg/kg in sites administering this dose in Part II. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up to the nearest milligram per institutional standard. There will be no dose modifications allowed.

During **Part I**, subjects may be dosed no less than 19 days between doses. If dosing is delayed, both nivolumab and ipilimumab must be delayed together. If dosing is resumed after a delay, both nivolumab and ipilimumab must be resumed on the same day. During **Part II**, subjects may be dosed no less than 12 days between doses.

Subjects may be dosed up to 3 days after the scheduled date if necessary. Subsequent dosing should be based on the actual date of administration of the previous dose of drug.

4.5.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of study drugs. See Section 4.5.7 for subsequent premedication recommendations following a nivolumab or ipilimumab-related infusion reaction.

4.5.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related AEs (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume (Section 4.5.5).

Nivolumab administration should be delayed for the following:

- Any Grade 2 non-skin, drug-related adverse event, with the exception of fatigue

- Grade 2 drug-related creatinine, AST, ALT, and/or total bilirubin abnormalities
- Grade 3 skin, drug-related adverse event
- Grade 3 drug-related laboratory abnormalities with the following exceptions:
  - Grade 3 lymphopenia or asymptomatic amylase or lipase does not require dose delay
  - Grade ≥ 3 AST, ALT, or total bilirubin will require dose discontinuation (see Section 4.5.6).
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

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

The algorithms recommended for utilization are included in the nivolumab IB and Appendix 1 of this protocol.

See Section 4.5.5 for the maximum dosing delay. As described in Section 4.5.3, refer to the Investigator's Brochure for management of AEs associated with immuno-oncology agents.

4.5.3 Management Algorithms for Immuno-Oncology Agents:

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration from AEs caused by other therapeutic classes. Nivolumab and ipilimumab are considered an I-O agent in this protocol. Timely recognition and early management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. BMS has adapted algorithms for use across immuno-oncology assets. These algorithms have led to successful resolution of toxicities with nivolumab monotherapy as well as in combination with ipilimumab. The algorithms are recommendations; there is flexibility to initiate more aggressive management when the investigator feels appropriate. Management algorithms can be found in Appendix 1 and have been developed to assist investigators in assessing and managing the following groups of AEs:

- Pulmonary
- Gastrointestinal
- Endocrine
- Hepatic
- Renal
- Skin

Early intervention with corticosteroids or IMM may be instituted under this protocol upon the investigator's clinical judgment.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in the Investigator's Brochure. While the ipilimumab Investigator Brochure contains safety

management algorithms for similar adverse events, the recommendations are to follow the nivolumab Investigator's Brochure algorithms for I-O agents in order to standardize the safety management.

4.5.4 Dose Modifications

Dose reductions and escalations are not permitted.

4.5.5 Criteria to Resume Treatment

Subjects may resume treatment with study drug 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
- For subjects with Grade 2 AST, ALT, or total bilirubin elevations, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.6) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment. Adrenal insufficiency ≥ Grade 3 requires discontinuation regardless of control with hormone replacement.

Subjects may resume treatment if the dose of systemic corticosteroids is 10 mg or less daily prednisone equivalent and immunosuppressive therapies (eg, infliximab) are not required.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the cycle schedule will be revised to meet the dosing window requirements (ie, the next scheduled dose will occur at a minimum of 19 days in Part I and a minimum of 12 days in Part II after the re-initiation of dosing). See Section 4.5.2 for the maximum dosing delay.

If treatment is delayed > 12 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.6.

As described in Section 4.5.3, refer to the nivolumab Investigator's Brochure for management of AEs associated with I-O agents.

During Part I, both nivolumab and ipilimumab should be resumed on the same day. However, if a nivolumab-related infusion reaction prevents subsequent infusion of ipilimumab on the same day, the dose of ipilimumab should be replaced as soon as possible. In such instances, at least

19 days must elapse between the replacement dose of ipilimumab and the administration of the next dose of nivolumab combined with ipilimumab.

If both nivolumab and ipilimumab are discontinued during Part I due to an AE, a subject may begin nivolumab monotherapy (Part II) providing the following conditions are met:

- The adverse event has resolved to Grade ≤ 1 or baseline within 12 weeks.
- Subjects had no prior life-threatening AEs.
- In investigator's opinion, the subject may derive a clinical benefit from continuation of nivolumab monotherapy treatment.
- Restrictions in Section 4.5.5, Criteria to Resume Treatment are met.
- Restrictions in Section 3.4, any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, non-palliative radiation therapy, or standard or investigational agents for treatment of cancer) are met.

4.5.6 Discontinuation Criteria

Discontinuation criteria apply for all drug-related AEs attributed to nivolumab, ipilimumab, or both.

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies
  - Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, myocarditis, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
  - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - Grade ≥ 3 drug-related AST, ALT, or total bilirubin requires discontinuation

        NOTE: In most cases of Grade 3 AST or ALT elevation, study drugs will be permanently discontinued. If the investigator determines a possible

favorable benefit/risk ratio that warrants continuation of study drug(s), a discussion between the investigator and the BMS Medical Monitor/designee must occur.

- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Any Grade 4 drug-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 neutropenia ≤ 7 days
  - Grade 4 lymphopenia or leukopenia or asymptomatic amylase or lipase
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
  - Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.
- Any dosing interruption lasting > 12 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related AEs are allowed.
  - Dosing interruptions > 12 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 > 12 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

As described in Section 4.5.3, refer to the nivolumab Investigator's Brochure for management of AEs associated with I-O agents.

4.5.7 Treatment of Nivolumab- or Ipilimumab-Related Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. 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 paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.

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

Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 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 1:1,000 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 from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or

generalized pruritus within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.5.8 Treatment Beyond Disease Progression

As described in Section 1.1.5, accumulating evidence indicated a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (PD).[53]

Subjects treated with the study drugs will be permitted to continue treatment beyond initial PD as assessed by the investigator's clinical judgment and local standards of care as long as they meet the following criteria:

- Investigator-assessed clinical benefit and do not have rapid disease progression
- Tolerance of study drug(s)
- Stable performance status
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression (eg, central nervous system [CNS] metastases).
- Subject provides written informed consent prior to receiving additional study treatment using an ICF describing any reasonably foreseeable risk or discomforts or other alternative treatment options
- A radiographic assessment/scan should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, stable disease, or continued PD. The assessment of clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment.

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

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

Global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at the time should be reported as symptomatic deterioration.

Every effort should be made to document objective progression (ie, radiographic confirmation) even after discontinuation of treatment.

The assessment of clinical benefit should take into account whether the subject is clinically deteriorating and unlikely to receive further benefit from continued treatment. All decisions to continue treatment beyond initial progression must be discussed in the study records, and subjects must sign a separate informed consent form to receive treatment beyond progression.

4.6 Blinding/Unblinding

Not applicable.

4.7 Treatment Compliance

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

4.8 Destruction of Study Drug

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

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

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

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

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

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

4.9 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Procedural Outline (CA209401)

Procedure	Screening Visit[a]	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	Assessed at screening visit prior to any procedures and reassessed prior to first dose.
Medical History	X	Documentation of mutation status (BRAF, NRAS, cKIT) if considered standard of care or if otherwise known.
Safety Assessments		
Physical Examination	X	Included height, weight, ECOG PS. Focused physical exam performed at screening, if clinically indicated.
ECOG Performance Status	X	ECOG PS 0-1 ECOG PS 2
Vital Signs and Oxygen Saturation	X	Temperature, BP, RR, O2 saturation by pulse oxymetry at rest (also monitor amount of supplement oxygen if applicable). Obtain vital signs at screening visit and within 72 hours of first dose.
Serious Adverse Events Assessment	X	
Adverse Events Assessment	X	No AE collection before first dose.
Assessment of Signs and Symptoms	X	After obtaining Informed Consent, assess all signs and symptoms within 14 days of first dose, prior to study treatment initiation.
[redacted]	[redacted]	[redacted]
Laboratory Tests	X	Chemistry tests performed locally within 14 days prior to first dose (unless otherwise specified): CBC with differential, chemistry (BUN or serum urea level, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, and glucose), AST, ALT, total bilirubin, alkaline phosphatase, albumin, LDH, TSH, free T3, free T4, and lipase. Within 28 days prior to first dose, hepatitis B surface

Table 5.1-1: Screening Procedural Outline (CA209401)

Procedure	Screening Visit[a]	Notes
		antigen (HBsAg) and hepatitis antibody (HCV Ab).
Pregnancy Tests	X	Performed within 24 hours prior to first dose for WOCBP only (serum or urine as required by the standard of care at the site). An extension of up to 72 hours prior to the first dose of nivolumab and ipilimumab is permissible in situations where results cannot be obtained within the standard 24 hour window. See Section 3.3.3 for the definition of Women of Childbearing Potential
Tumor Tissue Sample	X	May be archival. 1 paraffin block or a minimum of 10 FFPE unstained slides received by Central Lab prior to subject enrollment. (FNA and bone metastases samples not acceptable)
Additional Assessments		
[redacted]		[redacted]
Efficacy Assessments		
Screening/Baseline Tumor Assessments	X	Chest, abdomen, pelvis, brain, and other known sites of disease within 6 weeks of the first dose of study therapy. Subjects must have evaluable disease by CT or MRI per RECIST 1.1 criteria (radiographic tumor assessment performed within 6 weeks prior to first dose of study) or clinically apparent disease that the investigator to follow for response.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; CT, computerized tomography; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HBsAg, hepatitis B surface antigen; HCV Ab, hepatitis C antibody; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; O2, oxygen; PS, Performance Status; RECIST, Response Evaluation Criteria in Solid Tumors; RR, respiratory rate; TSH, thyroid stimulating hormone; WOCBP, women of child bearing potential

[a] Within 28 days ± 5 days before start of nivolumab and ipilimumab combination regimen

Table 5.1-2: On Study Assessments Part I: Cycles 1 Through 4 (Nivolumab Plus Ipilimumab)[a]

Procedure	Every Cycle (Every 3 weeks)	Every 2 Cycles (Every 6 Weeks)	Notes
Safety Assessments			
Physical Measurements (including PS)	X		Collect weight and ECOG PS within 72 hours prior to dosing. Focused physical exams should be performed as clinically indicated.
Vital Signs and Oxygen Saturation	X		Tests include temperature, BP, HR, RR, O2 saturation by pulse oxymetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms
Serious Adverse Event Assessments		---See notes---	Assessments are done during office visits and by weekly calls to subject during weeks the subject is not in the office for a clinic visit. Assessed using NCI CTCAE v 4.0. See Appendix 1.
Adverse Event Assessment		---See notes---	Assessments are done during office visits and by weekly calls to subject during weeks the subject is not in the office for a clinic visit. Assessed using NCI CTCAE v 4.0.
[redacted]	[redacted]		
Laboratory Tests: CBC with differential	X		CBCs with differential includes white blood cell count, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count. Laboratory tests should be completed and reviewed within 72 hours prior to dosing on infusion days.
Laboratory Test: Chemistry test	X		Chemistry tests include BUN or serum urea level, creatinine, sodium, potassium, calcium, chloride, amylase, lipase, glucose, phosphate, LDH, and magnesium.
Laboratory Test: Liver function tests	X		Liver function tests include AST, ALT, total bilirubin, alkaline phosphatase, albumin.
Laboratory Tests: Thyroid function tests		X	Thyroid function testing including TSH (free T3 and free T4 if abnormal results for TSH)
Pregnancy Test	X		Completed more frequently if required by local regulations (serum or blood as required by standard of care at the site). Pregnancy testing may be performed at home if an in-office visit is otherwise not required.

Table 5.1-2: On Study Assessments Part I: Cycles 1 Through 4 (Nivolumab Plus Ipilimumab)[a]

Procedure	Every Cycle (Every 3 weeks)	Every 2 Cycles (Every 6 Weeks)	Notes
Efficacy Assessments			
Tumor Scans		---See notes---	Initial tumor assessment, utilizing RECIST 1.1 criteria, is to be completed at Week 12 (±5 days). Further tumor assessments are recommended to be completed as required by local standards of care or at the investigator discretion and are recommended every 8 weeks.
Outcomes Assessments			
[redacted]		[redacted]	
Clinical Drug Supplies			
Administration of Study Drug	X		

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HR, heart rate; LDH, lactate dehydrogenase; LFT, liver function test; NCI CTCAE, National Cancer Institute Common Terminology Criteria for AEs; O2, oxygen; PS, Performance Status; NCI CTACE, National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors; RR, respiratory rate; TSH, thyroid stimulating hormone; TFT, thyroid function test.

Table 5.1-3: On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy)[a,b]

Procedure	Every Cycle (Every 2 weeks)	Every 2 Cycles (Every 4 weeks)	Every 3 Cycles (Every 6 weeks)	Every 4 Cycles (Every 8 weeks)	Notes
Safety Assessments					
Physical Measurements (including PS)	X				Collect weight and ECOG PS within 72 hours and review prior to dosing. Focused physical exams should be performed as clinically indicated.
Vital Signs and Oxygen Saturation	X				Tests include temperature, BP, HR, RR, O2 saturation by pulse oxymetry at rest (also monitor amount of supplemental oxygen if applicable) within 72 hours prior to dosing and at any time a subject has any new or worsening respiratory symptoms.
Serious Adverse Event Assessments	X				Assessed using NCI CTCAE v 4.0. See Appendix 1.
Adverse Event Assessment	X				Assessed using NCI CTCAE v 4.0
[redacted]	[redacted]				
Laboratory Tests: CBC with differential	X				As required by local standard of care or at the investigator's discretion. Includes white blood cell count, lymphocyte count, absolute neutrophil count, hemoglobin, hematocrit, and platelet count.
Laboratory Tests: Chemistry test	X				Includes blood urea nitrogen [BUN] or serum urea level, creatinine, sodium, potassium, calcium, chloride, amylase, lipase, glucose, phosphate, LDH, and magnesium
Laboratory Tests: Liver function test	X				Includes AST, ALT, total bilirubin, alkaline phosphatase, albumin.

Table 5.1-3: On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy)[a,b]

Procedure	Every Cycle (Every 2 weeks)	Every 2 Cycles (Every 4 weeks)	Every 3 Cycles (Every 6 weeks)	Every 4 Cycles (Every 8 weeks)	Notes
Laboratory Test: Thyroid function test			X		Includes TSH (free T3 and free T4 if abnormal results for TSH)
Pregnancy Test		X			Completed more frequently if required by local regulations (serum or blood as required by standard of care at the site). Pregnancy testing may be performed at home if an in-office visit is otherwise not required.
Efficacy Assessments					
Tumor Scans		---See notes---			Recommended to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks. Subjects with brain metastasis should have surveillance MRI approximately every 12 weeks or sooner if clinically indicated.
Outcomes Assessments					
[redacted]				[redacted]	[redacted]

Table 5.1-3: On-Treatment Assessments Part II: Cycles 5 and Beyond (Nivolumab Monotherapy)[a,b]

Procedure	Every Cycle (Every 2 weeks)	Every 2 Cycles (Every 4 weeks)	Every 3 Cycles (Every 6 weeks)	Every 4 Cycles (Every 8 weeks)	Notes
Clinical Drug Supplies					
Administration of Study Drug	X				

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood count; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HR, heart rate; LDH, lactate dehydrogenase; LFT, liver function test; NCI CTCAE, National Cancer Institute Common Terminology Criteria for AEs; O2, oxygen; PS, Performance Status; NCI CTACE, National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST, Response Evaluation Criteria in Solid Tumors; RR, respiratory rate; TSH, thyroid stimulating hormone; TFT, thyroid function test.

[a] If a dose is delayed, the procedures scheduled for that same time point should also be delayed to coincide with when that time point's dosing actually occurs.

[b] Cycle 5 begins 3 weeks after Cycle 4.

Table 5.1-4: Follow Up Assessments for Subjects who Discontinue in Part I[a]

Procedure	Every 4 Weeks (±7 days) through 100 Days after last dose of study drug	Notes
Safety Assessments		
Physical Exams	X	Collect weight and ECOG PS. Focused physical examination may be performed if clinically indicated and to assess for potential late emergent study drug related issues.
Vital signs and Oxygen Saturation	X	Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) at any time a subject has any new or worsening respiratory symptoms.
[redacted]	[redacted]	
Adverse Event Assessment	X	All nonserious AEs (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 to stabilization or reported as SAEs if they become serious.
Serious Adverse Event Assessments	X	All SAEs that occur during the screening period and within 100 days of discontinuation of dosing must be collected.
Laboratory Tests: CBC with differential	X	Includes WBC, lymphocytes, ANC, hemoglobin, hematocrit, platelet count.
Laboratory Tests: chemistry tests	X	Includes BUN or serum urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, amylase, lipase, and LDH.
Laboratory Tests: Liver function tests	X	Includes AST, ALT, total bilirubin, alkaline phosphate, albumin
Efficacy Assessments		
Subject survival status	---see notes---	May be accomplished by visit for the first 100 days and then by visit or phone for up to 2 years from the first dose of combination regimen therapy
Laboratory Tests: Thyroid function tests	X	Includes TSH (reflect to free T3 and free T4 if abnormal results)
Tumor scans	---see notes---	Tumor progression scans are recommended to be completed as required by local standards of care or at the investigator's discretion for up to 2 years.

Table 5.1-4: Follow Up Assessments for Subjects who Discontinue in Part I[a]

Procedure	Every 4 Weeks (±7 days) through 100 Days after last dose of study drug	Notes
Pregnancy Test in WOCBP	X	Completed more frequently if required by local regulations (serum or blood as required by standard of care at the site). Pregnancy testing may be performed at home if an in-office visit is otherwise not required.
Outcomes Assessments		
[redacted]	[redacted]	[redacted]

[a] Subjects who discontinue in Part I are recommended to be followed by direct contact (office visit) every 4 weeks (± 7 days) for up to 100 days from the last dose or should coincide with the date of discontinuation (±7 days) if the date of discontinuation is greater than 4 weeks (±7 days) after the last dose. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related AEs until resolved, AE symptoms return to baseline, or are deemed irreversible, for up to 2 years from the first dose or until lost to follow-up, withdrawal of study consent, or death, whichever comes first.

Table 5.1-5: Follow Up Assessments for Subjects who Discontinue in Part II

Procedure	FU-X01 (30 days ±7 days)	FU-X02 (70-84 days after FU-X01 ±7 days)	Follow-Up Visits after FU-X02. Every 24 weeks ±2 weeks	Notes
Safety Assessments				
Physical Examination	X	X		Collect weight and ECOG PS. Focused physical examination may be performed if clinically indicated and to assess for potential late emergent study drug related issues.
Vital signs and Oxygen Saturation	X	X		Temperature, BP, HR, RR, O2 saturation by pulse oximetry at rest (also monitor amount of supplemental oxygen if applicable) at any time a subject has any new or worsening respiratory symptoms.
[redacted]	[redacted]	[redacted]		
AEs Assessment	X	X	X	All nonserious AEs (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 to stabilization or reported as SAEs if they become serious.
Serious Adverse Events Assessments	X	X	X	All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing.
Laboratory Tests: CBC with differential	X	X		Includes WBC, lymphocytes, ANC, hemoglobin, hematocrit, platelet count.
Laboratory Tests: Chemistry tests	X	X		Includes BUN or serum urea, creatinine, sodium, potassium, calcium, magnesium, phosphate, chloride, glucose, amylase, lipase, and LDH.
Laboratory Tests: Liver function tests	X	X		Includes AST, ALT, total bilirubin, alkaline phosphate, albumin.

Table 5.1-5: Follow Up Assessments for Subjects who Discontinue in Part II

Procedure	FU-X01 (30 days ±7 days)	FU-X02 (70-84 days after FU-X01 ±7 days)	Follow-Up Visits after FU-X02. Every 24 weeks ±2 weeks	Notes
Laboratory Tests: Thyroid function tests	X	X		Includes TSH (reflect to free T3 and free T4 if abnormal results)
Pregnancy Test in WOCBP	X	X		Completed more frequently if required by local regulations (serum or blood as required by standard of care at the site). Pregnancy testing may be performed at home if an in-office visit is otherwise not required.
Efficacy Assessments				
Tumor Scans		---See Notes---		Tumor progression scans are recommended to be completed as required by local standards of care or at the investigator's discretion for up to 2 years.
Subject Survival Status	X	X	X	The first 2 visits are to be accomplished by onsite visit and then by visit or phone for up to 2 years from the first dose of combination regimen therapy.
Outcomes Assessments				
[redacted]	[redacted]	[redacted]		[redacted]

ANC, absolute neutrophil count; BP, blood pressure; CBC: complete blood count; WBC, white blood cells. Follow up period begins when the decision to discontinue a patient from study therapy is made (no further treatment with nivolumab) and continues from first dose of study therapy up to 2 years (+ 100 days following the last dose of study treatment) or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first..

Follow-up visit 1 (FU1) = 30 days from the last dose ±7 days or coincide with the date of discontinuation (± 7 days) if date of discontinuation is greater than 37 days after last dose, Follow-up visit 2 (FU2) = 84 days (± 7 days) from follow-up visit 1. Follow up visits 1 and 2 will occur within 100 days of last dose only after subject completes all study treatment. Beyond 100 days from the last dose of study therapy, subjects will be followed for ongoing drug-related AEs until resolved, AE symptoms returned to baseline, or are deemed irreversible, until lost to follow-up, or withdrawal of study consent or death.

5.1.1 Retesting During Screening Period

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

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

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

5.2 Study Materials

The site will provide:

- all required materials for the tests performed locally (ie, relevant to clinical laboratory tests)
- a well-calibrated scale for recording body weight
- a calibrated sphygmomanometer, and thermometer for vital sign assessments
- a monitored refrigerator
- all materials required for accurate source documentation of study activities.

BMS will provide:

- IVRS manual
- Nivolumab Investigator's Brochure and Ipilimumab Investigator's Brochure
- a BMS-approved protocol and any amendments or administrative letters (if required)
- case report forms (electronic or hard copy)
- nivolumab and ipilimumab
- validated and translated version of the EORTC QLQ-C30
- Pharmacy binder and pharmacy reference sheets

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions and mutation status. The baseline examinations should include weight, height, ECOG Performance Status, and should be performed within 28 days prior to first dose. Baseline signs and symptoms are those that are assessed within 14 days prior to first dose. Concomitant medications will be collected from within 14 days prior to the first dose through the study treatment period. Vital signs including temperature, blood pressure (BP), respiration rate, and oxygen saturation should be collected within 72 hours of first dose (see Table 5.1-1). A pregnancy test should be performed within 24 hours prior to first dose for WOCBP only (serum or urine as required by the standard of care at the site). An extension of up to 72 hours prior to the first dose of nivolumab

and ipilimumab is permissible in situations where pregnancy test results cannot be obtained within the standard 24 hour window.

Baseline local laboratory assessments should be done within 14 days prior to the first dose and include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), albumin, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, phosphate, glucose, lipase, TSH, Free T4, and Free T3. Hep B and C testing (HBV sAg and HCV RNA or Ab) should be done within 28 days prior to first dose.

The following safety assessments should be monitored every cycle, except where noted, starting with dosing until approximately 100 days following the discontinuation from study therapy, providing AEs have resolved:

- AEs continuously throughout the study
- Physical examination and physical measurements including weight and ECOG performance status
- Complete blood counts (CBCs) with differential, including WBC, lymphocyte count, ANC, hemoglobin, hematocrit, and platelet count. Laboratory tests should be completed and reviewed within 72 hours prior to dosing.
- Chemistry tests (BUN or serum urea level, creatinine, sodium, potassium, calcium, phosphate, chloride, magnesium, glucose, amylase, lipase, and LDH). Laboratory tests should be completed with 72 hours and reviewed prior to dosing. If sites are unable to obtain lipase results prior to dosing, dosing may still occur provided all other safety laboratory results including amylase are available and reviewed by the investigator prior to dosing.
- Liver function tests including AST, ALT, total bilirubin, alkaline phosphatase, albumin. Laboratory tests should be completed within 72 hours and reviewed prior to dosing.
- Thyroid function testing, including TSH (reflex to free T3 and free T4 if abnormal results), to be completed every 6 weeks. Laboratory tests should be completed within 72 hours and reviewed prior to dosing.
- Concomitant medications will be collected at the screening visit, throughout the study treatment period, and follow up.

Subjects will also receive a weekly phone call to report AEs on the weeks without study visits.

Follow up begins when the decision to discontinue study therapy is made (no further treatment with study drug) and is described in Table 5.1-4 and Table 5.1-5:

- Subjects who discontinue therapy in Part I are recommended to be followed by direct contact (office visit) every 4 weeks for up to 100 days after the last dose of regimen therapy. After completion of the onsite follow-up visits (for up to 100 days), subjects will be followed every 24 weeks ± 2 weeks for survival either by onsite visit or via telephone. OS will be followed from the start of therapy up to 2 years or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.

- For subjects who complete or discontinue therapy in Part II, subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug. After completion of the first 2 follow-up visits, subjects will be followed every 24 weeks ± 2 weeks for survival either by visit or phone. OS will be followed from the start of therapy up to 2 years (+ 100 days following the last dose of study treatment), or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first.
- For subjects who complete therapy in Part II (2 years of treatment), subjects will have 2 follow-up visits (office visits): one approximately 30 days after the last dose of study drug and one approximately 100 days after the last dose of study drug.

5.3.1 Imaging Assessment for the Study

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

5.4 Efficacy Assessments

Efficacy assessments include an initial tumor assessment at Week 12 (± 5 days) after first combination dose. Further tumor assessments are to be completed as required by local standards of care or at the investigator's discretion and are recommended every 8 weeks, as discussed in Table 5.1-2 and Table 5.1-3. Subjects will be followed for survival status in accordance with Table 5.1-4 and Table 5.1-5 for up to 2 years following the start of therapy (+ 100 days following the last dose of study treatment), or until death, withdrawal of study consent, or lost-to-follow-up, whichever comes first (see Section 5.3).

Study evaluations will take place in accordance with Table 5.1-2 and Table 5.1-3.

High resolution CT with oral or IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, please use local prophylaxis standards to obtain the assessment with contrast if at all possible or use an alternate modality. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Screening assessments should be performed within 6 weeks of first dose of study drug. Brain MRI is the preferred imaging method for evaluating CNS metastasis, and an assessment is required during screening in subjects with a known history of treated brain metastases. All known or suspected sites of disease (including CNS) should be assessed at screening and at subsequent assessments using the same imaging method and technique. If more than one method is used at screening, then the most accurate method (with RECIST 1.1 as the preferred method) should be used when recording data and should again be used for all subsequent assessments. Bone scan, PET scan, or ultrasound is not adequate for assessment of RECIST response. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is

identified in the target disease or when progression in bone is suspected. Previously treated CNS metastases are not considered measurable lesions for purposes of RECIST determined response.

Tumor measurements should be made by the same investigator or radiologist for each assessment whenever possible. Changes in tumor measurements and tumor responses to guide ongoing study treatment decisions should be assessed by the investigator.

5.4.1 Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

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

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

5.4.1.1 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.

5.4.1.2 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’).

5.4.2 Tumor Response Evaluation

5.4.2.1 Evaluation of Target Lesions

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

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

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

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

5.4.2.2 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.

5.4.2.3 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'

5.4.2.4 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).

5.4.3 Unequivocal Progression in Non-Target Disease

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

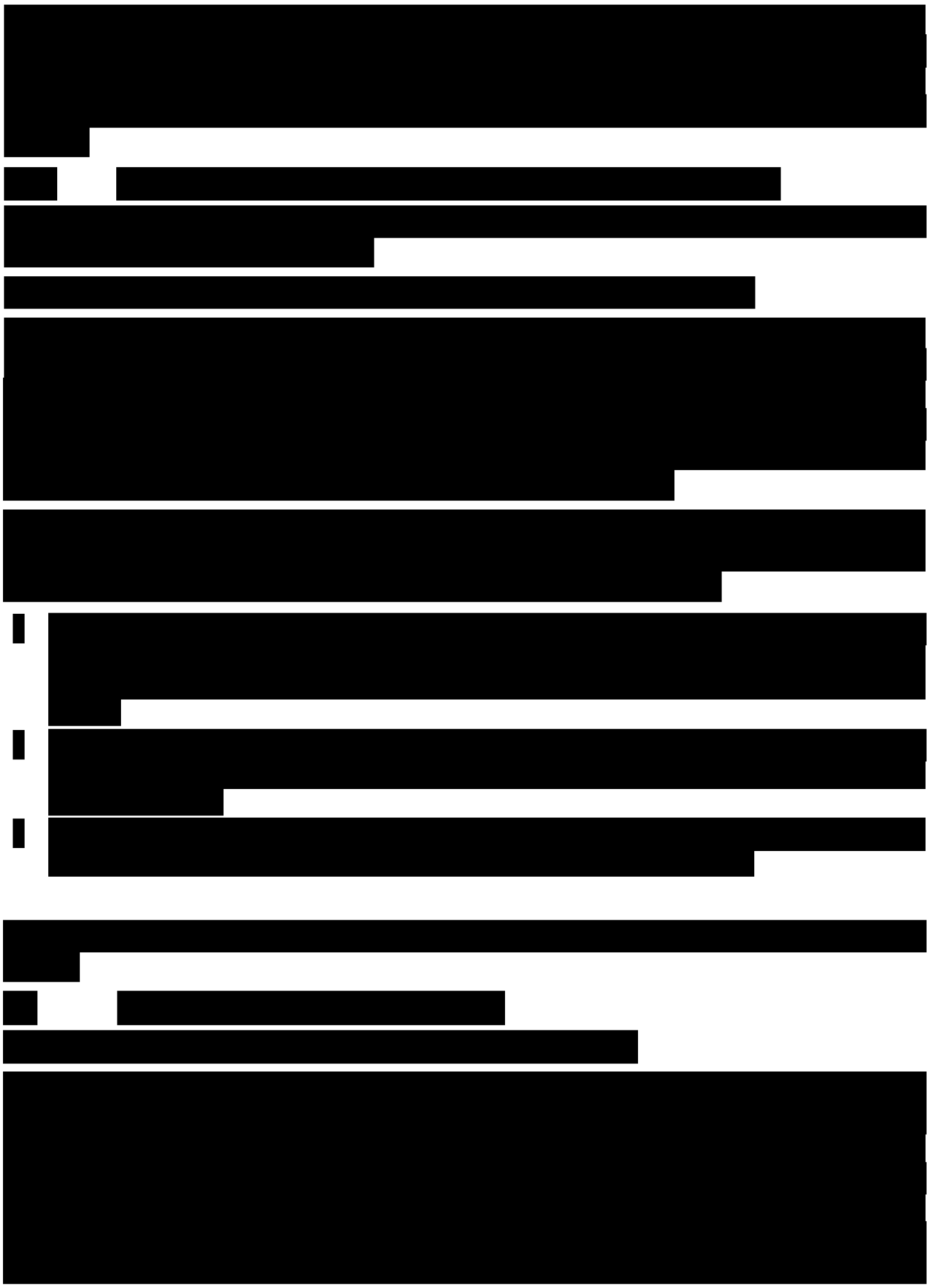
A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status

5.4.4 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.

[redacted]



[redacted]

5.8 Other 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 study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of study drug, whether or not considered related to the study drug.

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

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

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

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

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

For EEA countries the following will apply, unless alternative reporting modalities and mandated by local laws / guidelines:

- Investigator to report SAEs immediately (24 hrs) to sponsor. NSAE as per protocol specification.
- Sponsor records SAEs and AEs in a central database
- Sponsor to report SUSARs to HA, EC within 15 days (7 days for death / life threatening), unless local law / guidelines specify otherwise
- Sponsor to inform investigators of SUSARs in aggregate format (unless agreed otherwise)
- Annual Safety reports submitted to HA and EC
- SUSARs are submitted to EV from the EU PV Office in Braine.

- Impact on B/R shall be communicated in accordance with Directive 2001/20EC

For USA, requirements of FDA Code of Federal Regulations 21 CFR apply and for other countries safety reporting will be in accordance with local laws / guidelines.

Suspected Unexpected Serious Adverse Reaction is a serious adverse event that is both unexpected and related to an IMP or comparator IMP, for which expedited reporting to clinical investigators, Ethics Committees and Health Authorities is required (Previously known as ESR).

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

6.1 Serious Adverse Events

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

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

Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 100 days of discontinuation of dosing.

For subjects that are enrolled and never treated with study drug, report all SAEs that occur during the screening period and within 30 days of the date of enrollment.

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours of awareness of the event. SAEs must be recorded on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form (electronic or paper forms). The preferred method for SAE data reporting collection is through the eCRF. The paper SAE/pregnancy surveillance forms are only intended as a back-up option when the eCRF system is not functioning. In this case, the paper forms are to be transmitted via email or confirmed facsimile (fax) transmission to:

SAE Email Address: Refer to Contact Information list.

SAE Facsimile Number: Refer to Contact Information list.

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

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

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

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs must be followed to resolution or stabilization.

BMS will be reporting adverse events to regulatory authorities and ethics committees according to local applicable laws including European Directive 2001/20/EC and FDA Code of Federal Regulations 21 CFR Parts 312 and 320. A SUSAR (Suspected, Unexpected Serious Adverse Reaction) is a subset of SAEs and will be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

In most cases, the study drug will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

In the rare event that the benefit of continuing study drug is thought to outweigh the risk, after consultation with BMS, the pregnant subject may continue study drug after a thorough discussion of benefits and risk with the subject

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

1. AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
   AND
2. Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
   AND
3. No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

The Scientific Steering Committee (SSC) will closely review the safety data throughout the study to evaluate the risk/benefit ratio in general and for the separate prospective PS2 subgroup and for subjects treated by ipilimumab monotherapy experienced investigators following a predefined Safety Management Plan.

Safety Management Plan will include but not be limited to the following frequency and will be triggered by treated patients with ECOG PS-2

- Safety review: Safety review for all treated patients will take place when a minimum of 10 patients in ECOG PS2 subgroup have been dosed with at least 6 weeks of combination regimen therapy (nivolumab combined with ipilimumab) on study to assess safety in all subgroups and evaluate further enrollment into PS2 subgroup.
- Safety review: Safety review for all treated patients will take place when a minimum of 10 patients with at least 12 weeks of combination regimen therapy (nivolumab combined with ipilimumab) on study to assess safety in all subgroups.
- Subsequent safety reviews: According to the results of previous reviews, further monitoring and subsequent assessments and evaluation of safety will be conducted on a 12-week schedule and data will be provided.

The following data will be provided for safety review:

- Treatment-related AEs with focus on:
  - Drug-related SAEs in all subgroups
  - Immune-mediated, select adverse events: all grades in all treated patients

  - AEs leading to discontinuation
  - All treatment-related deaths
- ECOG performance status over time

If unexpected events occur, ad hoc telephone conferences with the SSC will be set up.

Review for risk/benefit assessment will be performed for all treated subjects. Initial review for the ECOG 0-1 subgroups is planned for the first 100 subjects who have been in the study for at least 6 months on study and should contain following parameters:

- Efficacy:
  - Response (based on initial tumor assessment) and overall clinical benefit
  - Symptomatic improvement
  - Survival benefit
- Safety:
  - Incidence (rate) and outcomes (time to and grade of resolution) of Grades 3-5, treatment-related AEs
  - Duration of immunosuppressant therapy for IMAE management
  - Change in ECOG Performance status over time

According to the results of the safety and risk/benefit reviews, further ones will be conducted on an as needed basis, and data will be provided.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Of 768 subjects who will be screened to receive first-line therapy for advanced disease with histologically confirmed stage III (unresectable) or stage IV melanoma, approximately 615 subjects will be treated with nivolumab and ipilimumab regimen. This sample size is based on the primary objective of the study: determining the incidence of high-grade (CTCAE v4.0 Grades 3-5), treatment-related, select adverse events of potentially immune-mediated etiology in subjects receiving first-line therapy for advanced disease. The sample size will allow for estimating an incidence of about 50% with a 95% CI of (46.06%, 54.11%) under 308 subjects with events among 615 treated subjects.

8.2 Populations for Analyses

- All enrolled subjects: all subjects who sign an informed consent form and are registered into the IVRS.
- All treated subjects: all subjects who receive any dose of study medicine. This is the primary population for safety and efficacy analyses.
- All response evaluable subjects: all treated subjects who have baseline and at least one on-study evaluable tumor measurement.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint is the incidence of high-grade (CTCAE v4.0 Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology (pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity).

8.3.2 Secondary Endpoint(s)

The secondary endpoints are:

- Incidence of all high-grade (Grades 3-5), select adverse events
- Median time to onset and median time to resolution (Grades 3-4) of select adverse events
- Resolution of an AE is a subject experiencing complete resolution or improvement to the baseline grade for the AE
- OS is defined as the time from first dosing date to the date of death. A subject who has not died will be censored at last known date alive.
- Safety and tolerability will be measured by the incidence of all AEs, treatment-related AEs, serious AEs, deaths, laboratory abnormalities, and select AEs such as pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity.
- The ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of all treated subjects. BOR is defined as the best response designation, recorded between the date of first dose and the date of the initial objectively documented tumor progression by the investigator or the date of subsequent therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR determination.
- Investigator-assessed PFS is defined as radiological evidence of progression, significant clinical symptomatic progression, or the need to introduce a non-study drug therapy.

[redacted]

8.4 Analyses

Descriptive statistics will be presented for each of the endpoints. The analysis of primary, secondary, and exploratory endpoints will be reported for the full safety analysis set (all treated subjects) and by subgroups based on ECOG PS, brain metastasis, ocular and mucosal melanoma, and investigator experience in treating with the nivolumab plus ipilimumab combination regimen.

8.4.1 Demographics and Baseline Characteristics

Demographics characteristic and disease characteristics at baseline will be summarized using descriptive statistics for all treated subjects and by cohort.

8.4.2 Efficacy Analyses

8.4.2.1 Secondary Analyses

OS will be summarized by Kaplan-Meier method for all treated subjects and by cohort. Median values of OS, along with 2-sided 95% CI using Brookmeyer and Crowley method, will be calculated.

The investigator-assessed ORR will be summarized by binomial response rates and their corresponding 2-sided 95% exact CIs using the Clopper-Pearson method. This analysis will be performed for all response evaluable subjects and by subgroup. The DOR will be summarized for subjects who achieve confirmed PR or CR using the Kaplan-Meier method. Median values of DOR, along with 2-sided 95% CI using Brookmeyer and Crowley method, will also be calculated.

The abovementioned OS, investigator-assessed ORR, and safety and tolerability will be conducted specifically for subjects with Performance Status 2, ocular or mucosal melanoma.

[redacted]

8.4.3 Safety Analyses

8.4.3.1 Primary Analyses

The number and percentage of subjects who report high-grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology will be summarized for all treated subjects overall. High-grade (Grade 3-5), treatment-related select adverse events will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term.

8.4.3.2 Secondary Analyses

The number and percentage of subjects who report high-grade (Grade 3-5), treatment-related, select adverse events of potentially immune-mediated etiology will be summarized for all treated subjects overall and by subgroup. High-grade (Grade 3-5), treatment-related, select adverse events will be tabulated using worst grade per CTCAE v4.0 criteria by system organ class and Medical Dictionary for Regulatory Affairs (MedDRA) preferred term. Time to onset and resolution of the events, dose of immune-modulating medications subjects received for the events, and the event by grade will also be tabulated for all treated subjects and by subgroups. Cumulative doses of immune-modulating agents will be summarized and reported.

All safety data will be listed and tabulated for all treated subjects. All AEs, treatment-related AEs, serious AEs, deaths, and select AEs such as pulmonary, gastrointestinal, skin, renal, hepatic, endocrine, infusion-related, or hypersensitivity will be summarized by system organ class and preferred term, and coded according to the most current version of MedDRA.

[redacted]

8.4.7 Other Analyses

Not applicable.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with, and be prepared by, BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Regulatory Authority(ies), if required by local regulations, 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. Certain CRF pages and/or electronic files may serve as the source documents.

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of study drug (inventoried and dispensed) is maintained at the study site to include investigational product and the following non-investigational product(s): NA. Records or logs must comply with applicable regulations and guidelines and should include:

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

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

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

9.2.3 Case Report Forms

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory abnormalities that are reported or identified during the course of the study.

For sites using the BMS electronic data capture tool, electronic CRFs will be prepared for all data collection fields except for fields specific to SAEs and pregnancy, which will be reported on the 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 as appropriate based on the following criteria:

- External Principal Investigator designated at protocol development
- Study Steering Committee chair or their designee
- Other criteria (as determined by the study team)

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

10 GLOSSARY OF TERMS

Term	Definition
Complete Abstinence	If one form of contraception is required, Complete Abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. If two forms of contraception is required, Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence. **Expanded definition** Complete abstinence as defined as complete avoidance of heterosexual intercourse is an acceptable form of contraception for all study drugs. This also means that abstinence is the preferred and usual lifestyle of the patient. This does not mean periodic abstinence (e.g., calendar, ovulation, symptothermal, profession of abstinence for entry into a clinical trial, post-ovulation methods) and withdrawal, which are not acceptable methods of contraception. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BMS	Bristol-Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CI	confidence interval
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HR	heart rate
HRT	hormone replacement therapy
ICH	International Conference on Harmonisation

Term	Definition
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug
I-O	Immuno-oncology agents
IRB	Institutional Review Board
IV	intravenous
kg	kilogram
LDH	lactate dehydrogenase
mg	milligram
min	minute
mL	milliliter
mmHg	millimeters of mercury
MTD	maximum tolerated dose
N	number of subjects or observations
Na+	sodium
N/A	not applicable
NIMP	non-investigational medicinal products
RBC	red blood cell
SAE	serious adverse event
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential