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Ex-US Non-IND
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Date: 11-Nov-2014
Revised Date 14-Oct-2020

CLINICAL PROTOCOL CA209238

A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence

(CheckMate 238: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 2238)

Revised Protocol Number: 06
Incorporates Administrative Letters 2 and 3

Medical Monitoring Contact Information	
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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	14-Oct-2020	The primary purpose of Revised Protocol 06 is to extend the collection of Overall Survival (OS) data for approximately 5 additional years. In addition, data associated with the primary, secondary, and exploratory efficacy outcomes (eg, melanoma recurrence data, data on development of new primary melanomas and non-melanoma cancers, subsequent anti-cancer therapies) will continue to be collected on Case Report Forms. Study drug-related serious adverse events (SAEs) will continue to be collected, whereas follow-up surveillance imaging assessments, plasma biomarker samples, and the EQ-5D questionnaire will no longer be required during extended follow-up.
Administrative Letter 03	15-Feb-2019	The purpose of this administrative letter is to change the Study Director for this study.
Administrative Letter 02	19-Dec-2017	The purpose of this administrative letter is to confirm that a surveillance assessment is required at the month 24 time point (relative to the first dose of study treatment).
Revised Protocol 05	26-Jan-2017	Incorporates Amendment(s) 18
Amendment 18	26-Jan-2017	The main purpose of this global amendment is to: • Add an interim analysis of RFS after all subjects have a minimum of 18 months of follow-up (approximately 350 RFS events are anticipated at this analysis). • Change the name and coordinates of the new Medical Monitor • Add the Mechanism for Action for Ipilimumab • Confirm that also blood samples from subjects receiving Ipilimumab will also be evaluated for development of Anti-Drug Antibody (ADA).
Revised Protocol 04	04-Aug-2016	Incorporates Amendment(s) 17
Amendment 17	04-Aug-2016	The main purpose of this global amendment is to: • Addition of Adrenocorticotropic hormone (ACTH) test at Week 45 in subjects receiving ipilimumab/ipilimumab-placebo at Week 48 (Note: All subjects will have completed 36 weeks of treatment prior to implementation of this amendment.) • Clarify that the minimum time between dosing visits is 12 days between Nivolumab administrations • Add information on surveillance scan requirements in case the patient discontinues and starts new systemic therapy. • Update the contraception section • Updates in the treatment algorithms
Revised Protocol 03	24-Feb-2016	Incorporates Amendment(s) 16

Document	Date of Issue	Summary of Change
Amendment 16	24-Feb-2016	The main purpose of this global amendment is to: 1) Increase the visit window from ± 2 days to ± 3 days for all dosing visits, except for Week 24, Week 36 and Week 48 where the visit window will increase from ± 2 days to ± 7 days. 2) Clarify that the minimum time between dosing visits is 12 days 3) Revise and clarify the Prohibited and /or Restricted Treatments 4) Update the acceptable methods of contraception
Revised Protocol 02	06-Aug-2015	Incorporates Amendment(s) 15
Amendment 15	06-Aug-2015	The main purpose of this global amendment is to: 1) Incorporate the definition of immune-mediated adverse events 2) Incorporate the Adverse Event Management Algorithms for Immuno-oncology Agents as an appendix, and updated terminology to be consistent throughout document 3) Clarify that follow-up of laboratory toxicities will continue until toxicities resolve, return to baseline, or are deemed irreversible based on on-site/local laboratory results. 4) Clarify that follow-up of immune-mediated adverse drug reactions will continue until toxicities resolve, return to baseline, or are deemed irreversible 5) Revise the discontinuation criteria to be consistent with the Nivolumab USPI 6) Revise the definition of recurrence free survival to include new primary melanoma 7) Add censoring rules for primary analysis of recurrence free survival 8) Clarify that subjects will continue to be followed for recurrences (until local or regional recurrences for all subjects and until distant recurrence for Stage III subjects) and survival
Revised Protocol 01	02-Apr-2015	Incorporates Amendment(s) 09 and Administrative Letter 01

Document	Date of Issue	Summary of Change
Amendment 09	02-Apr-2015	1) The main purpose of this global amendment is to clarify the age requirement to participate in the study as the inclusion of adolescents may not be appropriate per local regulations. 2) Additional clarifications have been made to other inclusion/exclusion criteria. 3) There is also a new requirement regarding additional sample collection (serum, and biopsy of affected organ) for biomarker analysis. This collection will be done upon occurrence of ≥ Grade 3 drug-related AE and lab abnormalities regarded as a drug related SAE when clinically safe and feasible 4) This amendment will also be used to implement recent changes in the program level protocol template as well as changes to the standard protocol model document 5) This amendment applies to all subjects
Administrative Letter 01	21-Jan-2015	1) IND Number 115,195 2) The title of Section 3.3.1, Item 2 should read “Target Population” 3) First survival follow-up visit will take place 3 months after Follow-up 2
Original Protocol	11-Nov-2014	Not applicable

SYNOPSIS

Clinical Protocol CA209238

Protocol Title: A Phase 3, Randomized, Double-blind Study of Adjuvant Immunotherapy with Nivolumab versus Ipilimumab after Complete Resection of Stage IIIb/c or Stage IV Melanoma in Subjects who are at High Risk for Recurrence.

(CheckMate 238: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 238)

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

Ipilimumab 10 mg/kg/dose IV q3 weeks x 4 doses, then 10 mg/kg/dose IV q12 weeks starting at week 24 or

Nivolumab 3 mg/kg/dose IV q2 weeks

Treat subjects until disease recurrence, unacceptable toxicity or subject withdrawal of consent, with a maximum of 1 year of treatment.

Study Phase: 3

Research Hypothesis: Treatment with nivolumab will improve recurrence-free survival as compared to ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV no evidence of disease (NED) melanoma who are at high risk for recurrence.

Objectives:

Primary:

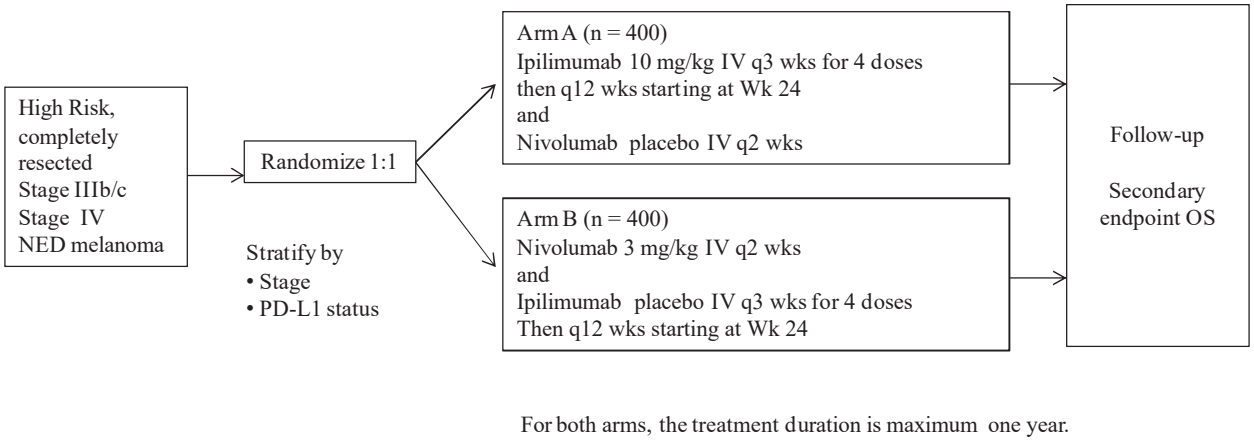
- To compare the efficacy, as measured by recurrence free survival (RFS), provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high-risk for recurrence.

Secondary:

- To compare the overall survival of nivolumab vs ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence;
- To assess the overall safety and tolerability of nivolumab and ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence;
- To evaluate whether PD-L1 expression is a predictive biomarker for RFS;
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

[redacted]

Study Design:



This is a Phase 3, randomized, double-blinded study of nivolumab versus ipilimumab in subjects (≥ 15 years) with complete resection Stage IIIb/c or Stage IV NED melanoma at high risk for recurrence.

Approximately 800 subjects will be randomized 1:1 and stratified by PD-L1 status (positive vs negative/indeterminate) and American Joint Committee on Cancer (AJCC) stage.

Dose reductions will not be allowed.

Subjects will be treated with one of the following:

Arm A: ipilimumab: 10 mg/kg IV q3 weeks for 4 doses, then q12 weeks starting at Week 24 with nivolumab placebo IV q2 weeks

Arm B: nivolumab 3mg/kg IV q2 weeks with ipilimumab placebo IV q3weeks for 4 doses, then q12 weeks starting at Week 24

All subjects will be treated until recurrence of disease, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1 year of treatment.

Note: As of Dec-2016, all subjects in both treatment groups were off study treatment.

Study Population: High risk, completely resected Stage IIIb/c and IV melanoma subjects.

Key Inclusion Criteria:

- At least 15 years of age
- Except: where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age.
- All subjects must be either Stage IIIb/c or Stage IV AJCC (7th edition) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens. Please refer to Appendix 1 for description of AJCC 7th editions of TNM and staging.
- If Stage III melanoma (whether Stage IIIb or IIIc) the subjects usually have clinically detectable lymph nodes that are confirmed as malignant on the pathology report and/or ulcerated primary lesions. Subjects who are "N2c" classification with 2-3 metastatic nodes and in transit metastases/satellites without metastatic nodes, or, "N3"classification with any "T" and 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes are eligible. The pathology report for both Stage IIIb and IIIc must be reviewed, signed and dated by the investigator; this process will be confirmed during the IVRS randomization call. Clinically detectable lymph nodes are defined as:
  1) a palpable node (confirmed as malignant by pathology)

2) a non-palpable but enlarged lymph node by CT scan (at least 15 mm in short axis) and confirmed as malignant by pathology
3) a PET scan positive lymph node of any size confirmed by pathology
4) evidence of pathologically macrometastatic disease in one or more lymph nodes defined by one or more foci of melanoma at least 1cm in diameter

If Stage IV melanoma, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.

- Complete resection of Stage III disease that is documented on the surgical and pathology reports or complete resection of Stage IV disease with margins negative for disease that is documented on the pathology report.
- Complete resection must be performed within 12 weeks prior to randomization
- All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include a CT scan of the neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c or Stage IV disease, and brain magnetic resonance (MRI) or CT (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
- Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression classification (positive, negative/or indeterminate) as determined by a central lab.

Key Exclusion Criteria:

- History of ocular/uveal melanoma
- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll.
- Subjects with previous non-melanoma malignancies are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ)
- Subjects with a condition requiring systemic treatment with either corticosteroids (≥ 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Prior therapy for melanoma except surgery for the melanoma lesion(s) and/or except for adjuvant radiation therapy (RT) after neurosurgical resection for central nervous system (CNS) lesions and except for prior adjuvant interferon (see qualifier below). Specifically subjects who received prior therapy with interferon, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) are not eligible.

  i) Prior treatment with adjuvant interferon is allowed if completed ≥ 6 months prior to randomization.

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

Study Drug for CA209238		
Medication	**Potency**	**IP/Non-IP**
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP
0.9% Sodium Chloride for Injection	N/A	IP
5% Dextrose for Injection	N/A	IP

Study Assessments: Recurrence-free survival is the primary endpoint of the trial. It is defined as the date between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. Subjects will be assessed for recurrence (until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects) by CT or MRI as follows:

- Screening.
- Treatment Period: Every 12 weeks (± 7 days) from first dose of study drug through 12 months (relative to the first dose of study drug)
- Follow-up Period:
  - Every 12 weeks (± 7 days) through 12 months for subjects who discontinued early from treatment (relative to the first dose of study drug)
  - Every 12 weeks (± 14 days) if > 12 months through 24 months (relative to the first dose of study drug)
  - Every 6 months (± 4 weeks) if > 24 months through and up to Year 5 (relative to the first dose of study drug). Although surveillance assessments will not be conducted beyond Year 5, data on recurrence of melanoma (loco-regional and distant), as well as development of new primary melanomas and non-melanoma cancers will continue to be collected in the respective Case Report Forms for an additional 5 years, for a total study duration of approximately 10 years.

Statistical Considerations:

Sample Size: The sample size is calculated to compare RFS between subjects randomized to receive nivolumab vs ipilimumab. Approximately 900 subjects have been randomized to the two treatment arms in a 1:1 ratio. The final analysis for RFS will take place after all subjects have a minimum of 36 months of follow-up and will take approximately 43.5 months from the start of the study. At 43.5 months, approximately 450 events are anticipated ensuring at least 85% power to detect a hazard ratio of 0.75 with an overall type I error of 0.05 (two-sided).

Endpoints:

Primary Endpoint: Recurrence Free Survival in all randomized subjects is the primary endpoint for this study.

Secondary Endpoint: Overall survival is a key secondary endpoint. If RFS superiority is demonstrated, OS will be tested hierarchically.

Analyses: The primary analysis of RFS in all randomized subjects will be conducted using a two-sided log-rank test stratified by PD-L1 status and stage. The hazard ratio and corresponding two-sided (1-adjusted α)% confidence interval (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a covariate, stratified by the above factors. RFS medians with 95% CIs and RFS rates at 6, 12, 18, 24, and 36 months with 95% CIs will be estimated using Kaplan-Meier methodology.

An interim analysis of RFS will be conducted after all subjects have a minimum of 18 months of follow-up. Approximately 350 RFS events are anticipated at this analysis. The stopping boundaries at the interim and final analyses will be derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. No interim analysis of OS will be performed at this time.

TABLE OF CONTENTS

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1 INTRODUCTION AND STUDY RATIONALE

[redacted]

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare the efficacy, as measured by RFS, provided by nivolumab versus ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence.

1.3.2 Secondary Objectives

- To compare the overall survival of nivolumab vs ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence.
- To assess the overall safety and tolerability of nivolumab and ipilimumab in subjects with completely resected Stage IIIb/c or Stage IV NED melanoma who are at high risk for recurrence.
- To evaluate whether PD-L1 expression is a predictive biomarker for RFS.
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.

[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:

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

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

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

For minors, according to local legislation, one or both parents or a legally acceptable representative must be informed of the study procedures and must sign the informed consent form approved for the study prior to clinical study participation. The explicit wish of a minor, who is capable of forming an opinion and assessing this information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

Minors who are judged to be of an age of reason must also give their written assent.

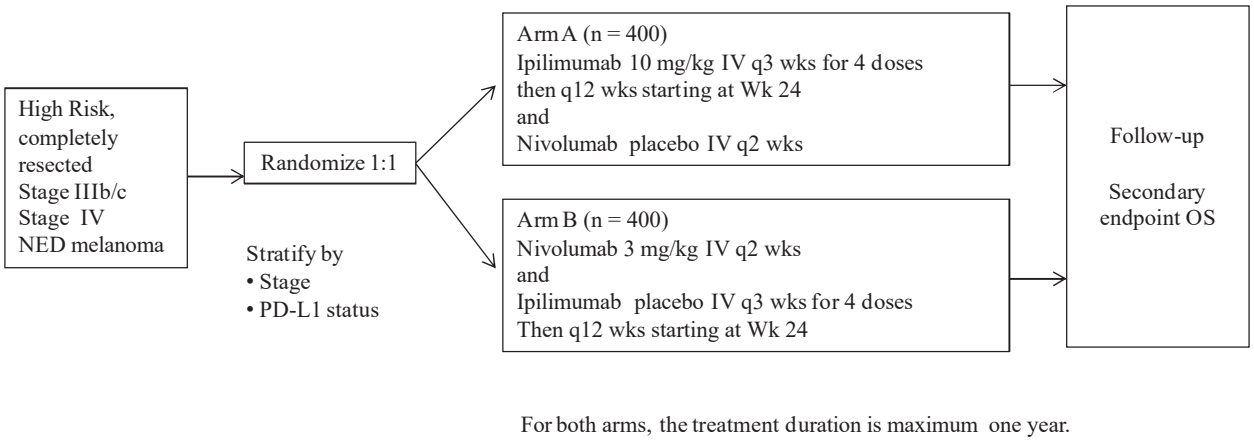
The rights, safety, and well-being of the study subjects are the most important considerations and should prevail over interests of science and society.

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

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

Figure 3.1-1: Study Design Schematic



The subjects will be treated in both arms until disease recurrence, unacceptable toxicity, or subject withdrawal of consent with a maximum of 1-year total duration of study medication.

Note: As of Dec-2016, all subjects in both treatment groups were off study treatment.

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

For a complete list of study required procedures, please refer to Section 5.

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the IVRS.
- Subject is assessed for complete study eligibility within the required timeframe found in Table 5.1-1.
- A pregnancy test for WOCBP should be documented within 24 hours prior to the start of the first dose of study medication.
- Tumor tissue must be received at the Central Laboratory for PD-L1 IHC testing in order for the subject to be randomized. PD-L1 status will be used as a stratification factor.
- If Stage III, the pathology reports of clinically detectable node(s) confirming malignancy must be reviewed, dated, and signed by the investigator prior to randomization.
- If Stage IV, the pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.

Treatment Phase:

- Following confirmation of the subject's eligibility, the randomization call to the IVRS can be made. The subject is randomly assigned to the ipilimumab 10 mg/kg arm and placebo arm (Arm A), or the nivolumab 3 mg/kg arm and placebo arm (Arm B).
- Within 3 business days from randomization the subject must receive the first dose of study medication (Day 1 of Week 1)
- On-study laboratory assessments should be drawn within 72 hours prior to dosing
- Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test every four weeks ± 1 week.
- PK samples and immunogenicity samples will be collected according to the schedule in Table 5.5-1
- Treated subjects will be evaluated for recurrence every 12 weeks ± 7 days
- Patient Reported Outcome (PRO) instruments must be completed after randomization, prior to the dose of study therapy and according to schedule in Table 5.1-2, Table 5.1-3, Table 5.1-4, and Table 5.1-6.
- This phase ends when the subject is discontinued early from study therapy or at a maximum of 1 year of treatment. For a complete list of reasons for treatment discontinuation, see Section 3.5.

Follow- up Phase:

- Begins after 1 year of treatment or when the decision is made to discontinue a subject from study therapy.
- Follow-up visits (See Table 5.1-3) include collection of PK/immunogenicity samples.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.
- Subjects who discontinue treatment for reasons other than recurrence will continue to have surveillance assessments (until local, regional, or distant recurrence (whichever comes first) recurrence for Stage IV subjects and until distant recurrence for Stage III subjects)
  - Surveillance assessments should occur every 12 weeks ± 7 days during the first year after randomization, every 12 weeks ± 14 days during the second year, every 6 months ± 4 weeks between Year 3 and Year 5 with the last assessment at Year 5.
  - Study-specified surveillance imaging assessments will be discontinued beyond Year 5. Data on recurrence of melanoma (loco-regional and distant), as well as development of new primary melanomas and non-melanoma cancers after Year 5 will continue to be collected in the respective Case Report Forms.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after the last dose of study medication.
- PRO instruments will be completed according to the schedule in Table 5.1-6.

The total duration of the study from start of randomization to the final survival follow-up visit is expected to be approximately 10 years.

The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the end of the study, BMS will not continue to provide BMS supplied study drug to subjects/investigators unless BMS chooses to extend the study. The investigator should ensure that the subject receives appropriate standard of care to treat the condition under study.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1) Signed Written Informed Consent

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

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

2) Target Population

a) All subjects must be either Stage IIIb/c or Stage IV American Joint Committee on Cancer (AJCC) Melanoma Staging (7th edition) and have histologically confirmed melanoma that is completely surgically resected in order to be eligible. Subjects must have been surgically rendered free of disease with negative margins on resected specimens. Please refer to Appendix 1 or description of AJCC 7th editions of TNM and staging.

i) If Stage III melanoma (whether Stage IIIb or IIIc) the subjects usually have clinically detectable lymph nodes that are confirmed as malignant on the pathology report and/or ulcerated primary lesions. Subjects who are “N2c” with 2-3 metastatic nodes and in transit metastases/satellites without metastatic nodes, or, “N3” classification with any “T” and 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes are eligible. The pathology report for both Stage IIIb and IIIc must be reviewed, signed and dated by the investigator; this process will be confirmed during the IVRS randomization call. Clinically detectable lymph nodes are defined as:

(1) A palpable node (confirmed as malignant by pathology)

(2) A non-palpable but enlarged lymph node by CT (at least 15 mm in short axis) and confirmed as malignant by pathology

(3) A PET positive lymph node of any size confirmed by pathology

(4) Evidence of pathologically macrometastatic disease in one or more lymph nodes defined by one or more foci of melanoma at least 1cm in diameter

ii) If Stage IV melanoma, the pathology report confirming negative margins must be reviewed, dated and signed by the investigator prior to randomization

- For CNS lesion(s), documentation, provided by a neurosurgeon, indicating that there has been complete resection of CNS lesion(s) will suffice as confirmation of negative margins

b) All melanomas, except ocular/uveal melanoma, regardless of primary site of disease will be allowed; mucosal melanomas are eligible.

c) Complete resection of Stage III disease that is documented on the surgical and pathology reports or complete resection of Stage IV disease with margins negative that is documented on the pathology report.

d) The last intervention demonstrating that the subject is free of disease must be performed within 12 weeks prior to randomization.

e) Subjects must not have received anti-cancer treatment (for example but not limited to, systemic, local, radiation, radiopharmaceuticals) for their melanoma.

3) Exceptions: Surgery for melanoma or/and post-resection brain RT if CNS metastases or/and prior treatment with adjuvant interferon under certain circumstances (as described in exclusion criterion 2di)

a) All subjects must have disease-free status documented by a complete physical examination and imaging studies within 4 weeks prior to randomization. Imaging studies must include CT scan of neck, chest, abdomen, pelvis, and all known sites of resected disease in the setting of Stage IIIb/c or Stage IV disease, and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).

b) The complete set of baseline radiographic images must be available before randomization.

c) ECOG performance status score of 0 or 1 (Appendix 2)

d) Tumor tissue from the resected site of disease must be provided for biomarker analyses. In order to be randomized, a subject must have a PD-L1 expression classification (positive, negative, or indeterminate) as determined by the central lab. If insufficient tumor tissue content is provided for analysis, acquisition of additional archived tumor tissue (block and /or slides) for the biomarker analysis is required.

e) Prior treated central nervous system (CNS) metastases must be without MRI evidence of recurrence for at least 4 weeks after treatment, subjects must be off immunosuppressive doses of systemic steroids (≥ 10 mg/day prednisone or equivalent) for at least 14 days prior to study drug administration, and must have returned to neurologic baseline post-operatively.

(1) The 4-week period of stability is measured after the completion of the neurologic interventions, ie surgery and/or radiation

f) In addition to neurosurgery to treat CNS metastases, adjuvant radiation after the resection of CNS metastasis is allowed. Immunosuppressive doses of systemic steroids (doses ≥ 10 mg/day prednisone or equivalent) must be discontinued at least 14 days before study drug administration

g) Prior surgery that required general anesthesia must be completed at least 4 weeks before study drug administration. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before study drug administration.

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

i) WBCs ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ 100 x 10^3/μL

iv) Hemoglobin ≥ 9.0 g/dL

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

vi) AST ≤ 3 x ULN

vii) ALT ≤ 3 x ULN

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

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

4) Age and Reproductive Status

a) Males and Females, ≥ 15 years of age

Except: where local regulations and/or institutional policies do not allow for subjects < 18 years of age (pediatric population) to participate. For those sites, the eligible subject population is ≥ 18 years of age

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

c) Women must not be breastfeeding

d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of study drug plus 30 days (duration of ovulatory cycle). The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. Given the blinded nature of this study, WOCBP should therefore use an adequate method to avoid pregnancy for a total of 5 months post-treatment completion (Appendix 3).

e) Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) plus 5 half-lives of the study drug (s) plus 90 days (duration of sperm turnover). The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. Given the blinded nature of this study, men should therefore use an adequate method of contraception for a total of 7 months post-treatment completion (Appendix 3).

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. (Refer to Appendix 3.)

3.3.2 Exclusion Criteria

1) Target Disease Exceptions

a) Subjects with carcinomatosis meningitis

b) History of ocular/uveal melanoma

2) Medical History and Concurrent Diseases

a) Subjects with previous non-melanoma malignancies are excluded unless a complete remission was achieved at least 3 years prior to study entry and no additional therapy is required or anticipated to be required during the study period (exceptions include but are not limited to, non-melanoma skin cancers; in situ bladder cancer, in situ gastric cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ)

b) Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll. For any cases of uncertainty, it is recommended that a BMS medical monitor be consulted prior to signing informed consent.

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

d) Prior therapy for melanoma except surgery for the melanoma lesion(s) and except adjuvant RT after neurosurgical resection for CNS lesions and except for prior adjuvant interferon (see qualifier below). Specifically subjects who received prior therapy with anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody (including ipilimumab or any other antibody or drug specifically targeting T cell co-stimulation or checkpoint pathways) are not eligible.

   i) Prior treatment with adjuvant interferon is allowed if completed ≥ 6 months prior to randomization

e) Treatment directed against the resected melanoma (eg, chemotherapy, targeted agents, biotherapy, or limb perfusion) that is administered after the complete resection other than adjuvant radiation after neurosurgical resection.

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.

3) Physical and Laboratory Test Findings

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

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

4) Allergies and Adverse Drug Reaction

a) History of Grade ≥ 3 allergy to human monoclonal antibodies

5) 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

c) Pregnant or nursing women

d) Psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the subject before registration in the trial

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

3.3.3 Women of Childbearing Potential

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

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the treatment and follow-up phases (before recurrence) of the study (unless utilized to treat a drug-related adverse event):

- Immunosuppressive agents - only until treatment discontinuation
- Immunosuppressive doses of systemic corticosteroids (except as stated in Section 3.4.2) - only until treatment discontinuation
- Any concurrent systemic anti-neoplastic therapy for the treatment of melanoma or a new malignancy (except as noted). Subjects who develop a new non-melanoma fully resectable malignancy (examples include but are not limited to: in situ bladder cancer, in situ gastric cancer, or in situ colon cancers; in situ cervical cancers/dysplasia; or breast carcinoma in situ; or prostate carcinoma) during the study may continue receiving study drugs if the only therapy required is hormonal therapy, surgery and/or radiation (and the surgery or radiation site does not overlap with a previous primary melanoma or melanoma metastasis location). Consultation with the medical monitor is required once a new malignancy is detected.

3.4.2 Permitted Therapy

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

Intravitreal injections of vascular endothelial growth (VEGF) inhibitors are permitted if used according to the approved ocular indication, such as macular degeneration.

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
- Recurrence (local, regional or distant)
- 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
- Unblinding a subject for any reason (emergency or non-emergency)
- Additional protocol specified reasons for discontinuation (see Section 4.5.7).

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.

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

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

3.6 Post Study Drug Study Follow up

In this study, RFS and OS are key endpoints. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 until death or the conclusion of the study.

BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window (Table 5.1-7). At the time of this request, each subject will be contacted to determine their survival status unless the subject has withdrawn consent for all contact.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. The site staff and

representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 STUDY DRUG

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

Table 4-1: Study Drugs for CA209238

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinded or Open Label	Packaging/ Appearance	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection	100 mg (10 mg/mL)	IP	Open Label[a]	10 mL/vial (5 or 10 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	IP	Open Label[a]	40 mL/vial (4 vials/carton)	Store at 2° - 8°C. Protect from light and freezing.
0.9% Sodium Chloride for Injection	N/A	IP	Open Label	Various (local commercial product)	As per active IP
5% Dextrose for Injection	N/A	IP	Open Label	Various (local commercial product)	As per active IP

[a] The term "open label" refers to the medication as it is upon receipt at the pharmacy. The trial will be conducted in a double-blinded fashion.

Premedications or medications used to treat infusion-related reactions should be sourced by the investigative sites if available and permitted by local regulations. Solutions used as diluent or placebo (ie, 0.9% Sodium Chloride Injection or 5% Dextrose Injection) should also be sourced by investigative sites if available and permitted by local regulations.

4.1 Investigational Product

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

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

In this protocol, investigational products are: nivolumab, ipilimumab, nivolumab placebo (0.9% sodium chloride injection or 5% dextrose injection), and ipilimumab placebo (0.9% sodium chloride injection or 5% dextrose injection).

4.2 Non-investigational Product

Not applicable.

4.3 Storage and Dispensing

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

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).

For study drugs not provided by BMS and obtained commercially by the site, storage should be in accordance with the product label

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab.

The unblinded pharmacist will obtain treatment assignment by IVRS and prepare blinded drug.

The infusion duration of nivolumab is 60 minutes and for ipilimumab 90 minutes.

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 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.

Once enrolled in IVRS, enrolled subjects that have met all eligibility criteria (the required tumor tissue received and result obtained by the central laboratory and the pathology report approved by the investigator) will be ready to be randomized through the IVRS. The randomization call will be performed by the unblinded pharmacy site staff. The following information is required for subject randomization:

- Subject number
- Date of birth
- PD-L1 evaluable status (Note that the result of PD-L1 positive vs PD-L1 negative/indeterminate is entered by the central laboratory vendor and both the site and the BMS study team remain blinded to the result)
- AJCC Stage and M classification
  - Stage IIIb/c
  - Stage IV M1a-M1b
  - Stage IV M1c.

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A ipilimumab + placebo or Arm B nivolumab + placebo stratified by the following factors:

- PD-L1 status
- AJCC stage (M classification if Stage IV).

The exact procedures for using the IVRS will be detailed in the IVRS manual.

4.5 Selection and Timing of Dose for Each Subject

First dose must be administered within 3 business days following randomization. When study drugs (ipilimumab or nivolumab) or matched placebos are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab or nivolumab-placebo is to be administered first. The second infusion will always be the ipilimumab or ipilimumab-placebo study drug, and will start no sooner than 30 minutes after completion of the nivolumab or nivolumab-placebo infusion.

Subjects may be dosed up to ± 3 days before or after the scheduled date if necessary. There should be a minimum of 12 days between 2 nivolumab/nivolumab-placebo administrations. For dosing visits of Week 24, Week 36 and Week 48, subjects may be dosed up to ± 7 days.

4.5.1 Dosing Schedule

The Dosing schedule is described in Table 4.5.1-1 and Table 4.5.1-2. Weight should be used to calculate the dose and if the weight differs ≥ 10% from baseline, the dose should be recalculated.

Table 4.5.1-1: Dosing Schedule

	Day 1 Week 1	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Day 1 Week 10	Day 1 Week 11	Day 1 Week 13
Arm A Ipilimumab + Nivolumab Placebo	3mg /kg Nivolumab-Placebo 10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	3mg /kg Nivolumab-Placebo 10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	Ipi 10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo
Arm B Nivolumab + Ipilimumab Placebo	3 mg/kg Nivolumab 10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab 10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab

	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Day 1 Week 21	Day 1 Week 23	Day 1 Week 24	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29
Arm A Ipilimumab + Nivolumab Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo
Arm B Nivolumab + Ipilimumab Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab

Table 4.5.1-2: Dosing Schedule

	Day 1 Week 31	Day 1 Week 33	Day 1 Week 35	Day 1 Week 36	Day 1 Week 37	Day 1 Week 39	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45
Arm A Ipilimumab + Nivolumab Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo
Arm B Nivolumab + Ipilimumab Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab	3 mg/kg Nivolumab

	Day 1 Week 47	Day 1 Week 48	Day 1 Week 49	Day 1 Week 51
Arm A Ipilimumab + Nivolumab Placebo	3 mg/kg Nivolumab-Placebo	10 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	3 mg/kg Nivolumab-Placebo
Arm B Nivolumab + Ipilimumab Placebo	3 mg/kg Nivolumab	10 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	3 mg/kg Nivolumab

If a subject cannot receive a dose within 3 days (or 7 days for dosing visits of Week 24, Week 36 and Week 48) of its scheduled administration date, the dose should be completely omitted. There should be a minimum of 12 days between 2 nivolumab/nivolumab-placebo administrations. When the subject is able to re-initiate treatment, dosing should resume at the time of the next scheduled dose. Missed doses will not be replaced.

4.5.2 Antiemetic Premedications

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

4.5.3 Dose Delay Criteria

Dose delays will not be allowed.

4.5.4 Dose Omission Criteria for Nivolumab or Ipilimumab

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

- Any Grade 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require dose omission
  - Please note that endocrine abnormalities, eg, TSH depression, are not considered isolated laboratory abnormalities since they involve symptoms at Grade 2. Therefore, endocrine adverse events of Grade 2 should lead to dose omission
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, or total bilirubin:
  - Grade 3 lymphopenia or leukopenia does not require dose omission
  - If a subject has baseline AST, ALT, or total bilirubin that is within normal limits, omit dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, omit dosing for drug-related Grade ≥ 3 toxicity
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose omission. It is recommended that the BMS medical monitor be consulted for Grade 3 amylase or lipase abnormalities.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants omitting the dose of study medication.

If the criteria to resume treatment (specified in Section 4.5.6) are met within the dosing window (Day 1, Week X ± 3 days, Week 24, Week 36 and Week 48 ± 7 days), then the dose may be given.

Note: per BMS standards, the term “interruption” is reserved for interruption of the actual IV infusion during administration. The terms omission and interruption should not be used synonymously when completing the CRF forms.

4.5.4.1 Adverse Event Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Early recognition and management of adverse events associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: gastrointestinal, renal, pulmonary, hepatic, endocrinopathies, skin and neurological. The management algorithms can be found in Appendix 4, and the nivolumab investigator brochure.

While the ipilimumab investigator brochure contains management algorithms for similar adverse events, the recommendations are to follow the adverse event management algorithms for I-O agents in Appendix 4 and the nivolumab investigator brochure in order to standardize the safety management across the blinded treatment arms.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Appendix 4 and in the nivolumab investigator brochure - Adverse Event Management Algorithms for I-O agents.

Immune-mediated AEs are specific events occurring within 100 days of the last dose (which includes pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine abnormalities [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]), regardless of causality, for which subjects received immunosuppressive medication for treatment of the event. The exception to the immunosuppressive medication criteria for IMAEs is endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression.

4.5.5 Dose Modifications

Dose reductions or dose escalations are not permitted.

All dose modification rules apply to both arms given the blinded nature of this study.

4.5.6 Criteria to Resume Treatment

All criteria to resume treatment for nivolumab and ipilimumab also apply for the placebo version of each agent, given the blinded nature of this study.

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

- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose omissions for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR Grade 2 total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.5.5) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, colitis, uveitis or neurological toxicity, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. However, if the treatment is withheld past the window period of the next scheduled timepoint per protocol to ensure adequate recovery from the adverse event or tapering of immunosuppression, the dosing should continue to be withheld until the subsequent scheduled timepoint.

If treatment is withheld > 6 weeks from the last dose, the subject must be permanently discontinued from study therapy, except as specified in Section 4.5.7.

4.5.7 Discontinuation Criteria

All discontinuation criteria for nivolumab and ipilimumab also apply for the placebo version of each agent, given the blinded nature of this study.

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 3 weeks OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
  - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
      - AST or ALT > 8 x ULN
      - Total bilirubin > 5 x ULN
      - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

- Creatinine greater than 6 times ULN
- Any severe or Grade 3 immune-mediated adverse reaction that recurs on reintroduction of nivolumab or ipilimumab, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 immune-mediated adverse drug reactions that do not recover to Grade 1 or resolve within 12 weeks after the last dose of study drug
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. It is recommended to consult with the BMS Medical Monitor for Grade 4 amylase or lipase abnormalities.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Dosing that is withheld > 6 weeks from the last dose with the following exceptions:
  - Dosing omissions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing omission period lasting > 6 weeks from the last dose, the BMS medical monitor must be consulted.
  - Dosing omissions > 6 weeks from the last dose that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing omission period lasting > 6 weeks from the last dose, the BMS medical monitor must be consulted.
- 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.
- Tumor surveillance assessments, QoL questionnaires collection and biomarker sampling should continue as per protocol even if dosing is omitted.

4.5.8 Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Since nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, 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 National Cancer Institute Common Terminology Criteria for Adverse Events (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 or ipilimumab administrations.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, 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 pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.6 Blinding/Unblinding

Blinding of treatment assignment is critical to the integrity of this clinical study. The management of adverse events for either nivolumab or ipilimumab is the same, according to the harmonized

adverse event management algorithms for I-O agents available in Appendix 4 and the nivolumab investigator brochure. However, in the event of a medical emergency or pregnancy in an individual subject in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the investigator. The subject's safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

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

Any request to unblind a subject for non-emergency purposes should be discussed with the Medical Monitor. For example, for subjects that have recurrence and discontinue treatment the investigator may require knowledge of which treatment arm they were assigned to in order to appropriately select any post-recurrence subsequent therapy. See Section 1.4.8.5.

For this study, the method of unblinding is IVRS.

The Principal Investigator should only call in for unblinding AFTER the decision to discontinue the subject has been made.

For information on how to unblind for emergency, please consult the IVRS manual.

In cases of accidental unblinding, contact the Medical Monitor and ensure every attempt is made to preserve the blind.

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

To further minimize bias, the sponsor central study team and the investigative clinical site staff are blinded to results from PD-L1 analysis.

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 standard operating procedures (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 (CA209238)

Procedure	Screening Visit (Day -28 till Day -1 prior to Randomization)	Notes
Eligibility Assessments		
Informed Consent	x	
Inclusion/Exclusion Criteria	x	All inclusion/exclusion criteria should be assessed during screening and confirmed prior to randomization.
Medical History	x	
Review of pathology report	x	Stage III: The pathology report must be reviewed, signed and dated by the investigator prior to randomization. Stage IV: The pathology report confirming negative margins must be reviewed, dated, and signed by the investigator prior to randomization.
[redacted]	[redacted]	[redacted]
Safety Assessments		
Physical Examination	x	Including height
Vital Signs	x	Including weight, blood pressure (BP), heart rate (HR), temperature
Oxygen saturation	x	By pulse oximetry at rest and after exertion
Performance Status (ECOG)	x	Within 14 days prior to randomization
Assessment of Signs and Symptoms	x	Within 14 days prior to randomization
Electrocardiogram (ECG)	x	Within 14 days prior to randomization

Table 5.1-1: Screening Procedural Outline (CA209238)

Procedure	Screening Visit (Day -28 till Day -1 prior to Randomization)	Notes
Laboratory Tests	x	On site/local complete blood count (CBC) w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, amylase, lipase, blood urea nitrogen (BUN) or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, endocrine panel (TSH, Free T4, Free T3) within 14 days prior to randomization. Hep B/C (HBV sAG, HCV antibody or HCV RNA) within 28 days prior to randomization
[redacted]	[redacted]	[redacted]
Pregnancy Test	x	WOCBP only
Efficacy assessment		
Surveillance assessments	x	CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions).
Other		
IVRS call	x	

Table 5.1-2: On-Treatment Assessments Week 1 - Week 9 (CA209238)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	To be performed within 72 hours prior to dosing
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry at rest and after exertion prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests	x			x		x	Within 72 hrs prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3) Note: Laboratory tests do not need to be repeated if performed within 14 days prior to first dose
Pregnancy Test	x			x		x	Within 24 hours prior to the initial administration of study drug, then every 4 weeks ± 1 week. Serum or Urine
[redacted]	[redacted]				[redacted]		[redacted]
[redacted]							
[redacted]	[redacted]				[redacted]		[redacted]

Table 5.1-2: On-Treatment Assessments Week 1 - Week 9 (CA209238)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
[redacted]							
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]	[redacted]			[redacted]		[redacted]
[redacted]	[redacted]						[redacted]
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for Stage IV subjects and until distant recurrence for Stage III subjects)						CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.

Table 5.1-2: On-Treatment Assessments Week 1 - Week 9 (CA209238)

Procedure	Day 1 Week 1	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 7	Day 1 Week 9	Notes
Study Drug							
IVRS Randomize	x						
Dispense Study Treatment (Active drug or placebo - blinded)	x	x	x	x	x	x	First dose to be administered within 3 business days of randomization. See Section 4.3. Subsequent doses may be administered within 3 days before or after the scheduled date if necessary.
Outcome Research Assessments							
EORTC-QLQ-C30	x			x	x		Prior to dosing. D1W1 should be completed after randomization but prior to dosing.
[redacted]	[redacted]			[redacted]	[redacted]		
[redacted]	[redacted]			[redacted]	[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-3: On-Treatment Assessments Week 10 - Week 19 (CA209238)

Procedure	Day 1 Week 10	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	Within 72 hours prior to dosing
Vital Signs	x	x	x	x	x	x	Including BP, HR, temperature
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry at rest and after exertion prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously						
[redacted]							
Laboratory Tests			x		x		Within 72 hrs prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test			x		x		Every 4 weeks ± 1 week. Serum or Urine
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							

Table 5.1-3: On-Treatment Assessments Week 10 - Week 19 (CA209238)

Procedure	Day 1 Week 10	Day 1 Week 11	Day 1 Week 13	Day 1 Week 15	Day 1 Week 17	Day 1 Week 19	Notes
[redacted]							
[redacted]							
[redacted]							
[redacted]							
[redacted]							
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for Stage IV subjects; until distant recurrence for Stage III subjects)						CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Dispense Study Treatment (Active drug or placebo - blinded)	x	x	x	x	x	x	See Section 4.3. Subsequent doses may be administered within 3 days before or after the scheduled date if necessary.
Outcome Research Assessments							
EORTC-QLQ-C30		x			x		Prior to dosing
[redacted]							
[redacted]							
[redacted]							

Table 5.1-4: On-Treatment Assessments Week 21 - Week 29 (CA209238)

Procedure	Day 1 Week 21	Day 1 Week 23	Day 1 Week 24	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	Within 72 hours prior to dosing
Vital Signs	x	x	x	x	x	x	
Weight and performance status	x	x	x	x	x	x	Within 72 hours prior to dosing
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry at rest and after exertion prior to dosing
Adverse Events Assessment	Continuously						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests	x			x		x	Within 72 hrs prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test	x			x		x	Every 4 weeks ± 1 week. Serum or Urine
[redacted]		[redacted]					[redacted]
[redacted]							
[redacted]		[redacted]					[redacted]

Table 5.1-4: On-Treatment Assessments Week 21 - Week 29 (CA209238)

Procedure	Day 1 Week 21	Day 1 Week 23	Day 1 Week 24	Day 1 Week 25	Day 1 Week 27	Day 1 Week 29	Notes
[redacted]							
[redacted]	[redacted]						
[redacted]				[redacted]			[redacted]
[redacted]	[redacted]						[redacted]
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for Stage IV subjects and until distant recurrence for Stage III subjects)						CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Dispense Study Treatment (Active drug or placebo - blinded)	x	x	x	x	x	x	See Section 4.3. Subsequent doses may be administered within 3 days (7 days for Week 24) before or after the scheduled date if necessary
Outcome Research Assessments							
EORTC-QLQ-C30				x			Prior to dosing
[redacted]				[redacted]			
[redacted]				[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-5: On-Treatment Assessments Week 31 - Week 39 (CA209238)

Procedure	Day 1 Week 31	Day 1 Week 33	Day 1 Week 35	Day 1 Week 36	Day 1 Week 37	Day 1 Week 39	Notes
Safety Assessments							
Targeted Physical Examination	x	x	x	x	x	x	Within 72 hours prior to dosing
Vital Signs	x	x	x	x	x	x	
Oxygen saturation	x	x	x	x	x	x	By pulse oximetry at rest and after exertion prior to dosing
Weight and performance status	x	x	x	x	x	x	Within 72 hours prior to dosing
Adverse Events Assessment	Continuously						
[redacted]							
Laboratory Tests		x			x		Within 72 hrs prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test		x			x		Every 4 weeks ± 1 week. Serum or Urine
[redacted]							[redacted]
[redacted]							
[redacted]							[redacted]

Table 5.1-5: On-Treatment Assessments Week 31 - Week 39 (CA209238)

Procedure	Day 1 Week 31	Day 1 Week 33	Day 1 Week 35	Day 1 Week 36	Day 1 Week 37	Day 1 Week 39	Notes
[redacted]							
[redacted]	[redacted]						
[redacted]					[redacted]		[redacted]
[redacted]	[redacted]						[redacted]
Efficacy Assessments							
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for Stage IV subjects and until distant recurrence for Stage III subjects)						CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV, and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug							
Dispense Study Treatment (Active drug or placebo - blinded)	x	x	x	x	x	x	See Section 4.3. Subsequent doses may be administered within 3 days (7 days for Week 36) before or after the scheduled date if necessary.
Outcome Research Assessments							
EORTC-QLQ-C30					x		Prior to dosing
[redacted]					[redacted]		
[redacted]					[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-6: On-Treatment Assessments Week 41 - Week 51 (CA209238)

Procedure	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45	Day 1 Week 47	Day 1 Week 48	Day 1 Week 49	Day 1 Week 51	Notes
Safety Assessments								
Targeted Physical Examination	x	x	x	x	x	x	x	Within 72 hours prior to dosing
Vital Signs	x	x	x	x	x	x	x	
Weight and performance status	x	x	x	x	x	x	x	Within 72 hours prior to dosing
Oxygen saturation	x	x	x	x	x	x	x	By pulse oximetry at rest and after exertion prior to dosing
Adverse Events Assessment	Continuously							
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Laboratory Tests	x		x			x		Within 72 hrs prior to dosing to include CBC w/differential, AST, ALT, ALP, T. Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3) ACTH at Week 45 in subjects receiving ipilimumab/ ipilimumab-placebo at Week 48 (note that all subjects will have completed 36 weeks at the time of implementation)
Pregnancy Test	x		x			x		Every 4 weeks ± 1 week. Serum or Urine.
[redacted]				[redacted]				[redacted]
[redacted]								
[redacted]				[redacted]				[redacted]

Table 5.1-6: On-Treatment Assessments Week 41 - Week 51 (CA209238)

Procedure	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45	Day 1 Week 47	Day 1 Week 48	Day 1 Week 49	Day 1 Week 51	Notes
[redacted]								
[redacted]								
[redacted]								
[redacted]								
Efficacy Assessments								
Surveillance Assessments	Every 12 weeks (± 7 days) from first dose of study treatment through 12 months (until local, regional, or distant recurrence [whichever comes first] for Stage IV subjects and until distant recurrence for Stage III subjects)							CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline.
Study Drug								
Dispense Study Treatment (Active drug or placebo - blinded)	x	x	x	x	x	x	x	See Section 4.3. Subsequent doses may be administered within 3 days (7 days for Week 48) before or after the scheduled date if necessary. Note: As of Dec-2016, all subjects in both treatment groups were off study treatment.
Outcome Research Assessments								
EORTC-QLQ-C30						x		Prior to dosing
[redacted]								
[redacted]								

Table 5.1-6: On-Treatment Assessments Week 41 - Week 51 (CA209238)

Procedure	Day 1 Week 41	Day 1 Week 43	Day 1 Week 45	Day 1 Week 47	Day 1 Week 48	Day 1 Week 49	Day 1 Week 51	Notes
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

Table 5.1-7: Follow-Up Procedural Outline (CA209238)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
Safety Assessments			
Targeted Physical Examination	x		
Adverse Events Assessment	x	x	See Section 6.2.1. Immune-mediated adverse reactions should be followed until stabilization. Nonimmune-mediated adverse reactions should be followed until resolution or stabilization.
Laboratory Tests	x		Laboratory toxicities (eg, suspected drug induced liver enzyme elevations) will be monitored during the follow-up phase, based on results from on-site/local labs, until all study drug related toxicities resolve, return to baseline, or are deemed irreversible.
Pregnancy Test	x		Serum or urine
[redacted]	[redacted]		[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Outcome Research Assessments			
EORTC-QLQ-C30	x		
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		

Table 5.1-7: Follow-Up Procedural Outline (CA209238)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
Efficacy Assessments			
Surveillance Assessment	• Every 12 weeks (± 7 days) < 12 months • Every 12 weeks (± 14 days) > 12 months through 24 months • Every 6 months (± 4 weeks) > 24 months through and up to Year 5 Until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects. All time points are relative to the first dose of study treatment.		CT scan neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Use same imaging method as was used at screening/baseline. Note: If a subject starts systemic therapy for melanoma recurrence after study drug discontinuation, follow-up scans should be discontinued. If a subject starts systemic therapy for a new non-melanoma tumor after study drug discontinuation, follow-up scans can be done as per standard of care. **Effective Revised Protocol 06:** Although study-specified surveillance assessments will not be conducted beyond Year 5, data on recurrence of melanoma (loco-regional and distant), as well as development of new primary melanomas and non-melanoma cancers will continue to be collected in the respective Case Report Forms. Subjects will be queried for this data during the routine survival status follow-up. This data will also be collected retrospectively to account for any time interval between the subject's Year 5 time point and approval of Revised Protocol 06 by ECs/IRBs.
Survival status			
Survival status	x	x	Every 3 months (± 14 days), maybe accomplished by visit or phone contact,[c] to include subsequent anti-cancer therapy. The frequency and mode of contact applies to the extended follow-up period as well. This data will be collected retrospectively to

Table 5.1-7: Follow-Up Procedural Outline (CA209238)

Procedure	Follow-up, Visits 1 and 2[a]	Survival, Follow up Visits[b]	Notes
			account for any time interval between the subject's Year 5 time point and approval of Revised Protocol 06 by ECs/IRBs.
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[a] Follow-up visit 1 (FU1) = 30 days (± 7 days) from the last dose or coincide with the date of discontinuation (± 7days) 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

[b] First Survival Follow-up visit 3 months (± 14 days) after FU2

[c] Phone contacts during the survival follow-up visits are only allowed at time periods between surveillance assessment visits.

5.1.1 Retesting During Screening or Lead-in Period

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

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

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

5.2 Study Materials

- NCI CTCAE version 4.0
- Nivolumab Investigator Brochure
- Ipilimumab Investigator Brochure
- Pharmacy binder
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens
- Site manual for operation of IVRS, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- PRO instruments.

5.3 Safety Assessments

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline examinations should include weight, height, ECOG Performance Status, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion and should be performed as noted in Table 5.1-1 Notes. Baseline signs and symptoms are those that are assessed within 14 days prior to randomization. Concomitant medications will be collected from within 14 days prior to randomization through the study treatment period and follow-up visits 1 and 2. (See Tables from Section 5.1.) During the Survival Follow-up visits subsequent only anti-cancer therapy will be collected.

Baseline local laboratory assessments should be done within 14 days prior to randomization to include: CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH, Free T4, Free T3; Hep B and C testing (HBV sAg, HCV RNA, HCV antibodies) should be assessed within 28 days prior to randomization (Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then every 4 weeks (± 1 week) during the treatment phase.

Subjects will be evaluated for safety if they have received any study drug. Toxicity assessments will be continuous during the treatment phase. During the safety follow-up phase Table 5.1-7, toxicity assessments should be done in person. Once subjects reach the survival follow-up phase either in person or documented telephone calls (telephone calls are only allowed during times where no surveillance assessments are to be done) to assess the subject's status are acceptable.

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

On-study weight and ECOG Performance status and vital signs should be assessed on at each on-study visit .Vital signs should also be taken as per institutional standard of care prior to, during and after dosing. Oxygen saturation by pulse oximetry at rest and after exertion should be assessed at each on study visit prior to dosing. The start and stop time of the blinded infusions should be documented. Physical examinations are to be performed as clinically indicated. If there are any new or worsening clinically significant changes since the last exam, report changes on the appropriate non-serious or serious adverse event page.

On study local laboratory assessments should be done within 72 hours prior to dosing (laboratory tests should not be repeated if performed within 14 days prior to the first dose) to include; CBC w/differential, LFTs (ALT, AST, total bilirubin, alkaline phosphatase), BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, amylase, lipase, TSH with reflexive Free T4, Free T3. Adrenocorticotropic hormone (ACTH) will be assessed at Week 45 prior to ipilimumab/ ipilimumab placebo administration at Week 48, since all subjects will be past the 36 weeks' timepoint. Additional measures including non-study required laboratory tests should be performed as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug inducted liver enzyme elevations) will be monitored during the follow-up phase via on site/local labs until all study drug related toxicities resolve, return to baseline or are deemed irreversible.

Oxygen saturation by pulse oximetry should be obtained prior to each dosing and at any time a subject has any new or worsening respiratory symptoms. Accurate recording and documentation of oxygen saturation at two different activity levels is important because drug-related pulmonary toxicity can present initially as lower than baseline oxygen saturation. A reading at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the investigator, but should remain consistent for each individual subject throughout the study. If the subject's status changes, the investigator can alter the extent of exertion based on their medical judgment. If a subject shows changes on pulse oximetry or other pulmonary related signs (hypoxia, fever) or symptoms (eg, dyspnea, cough, fever) consistent with possible pulmonary adverse events, the subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in Appendix 4 or the nivolumab investigator brochure.

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

5.3.1 Imaging Assessment for the Study

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

5.4 Efficacy Assessments

Study evaluations will take place in accordance with the flow charts in Section 5. Baseline disease assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. This includes a CT scan of neck, chest, abdomen, pelvis and all known sites of resected disease in the setting of Stage IIIb/c and Stage IV, and brain MRI (brain CT allowable if MRI is contraindicated or if there is no known history of resected brain lesions). Subjects will be evaluated for presence or continued lack of tumor until local, regional, or distant recurrence (whichever comes first) for Stage IV subjects and until distant recurrence for Stage III subjects beginning 12 weeks (± 7 days) relative to the first dose of study treatment, and will continue to have surveillance assessment every 12 weeks (± 7 days) for the first 12 months. From > 12 months to 24 months after randomization, efficacy assessments should be every 12 weeks (± 14 days). From > 24 months until Year 5 after first dose of study treatment, efficacy assessments should be performed every 6 months (± 4 weeks).

If a subject starts systemic therapy for melanoma recurrence after study drug discontinuation, follow-up scans should be discontinued. If a subject starts systemic therapy for a new non-melanoma tumor after study drug discontinuation, follow-up scans can be done as per standard of care.

5.4.1 Definitions

Recurrence is defined as the appearance of one or more new melanoma lesions, which can be local, regional, or distant in location from the primary resected site.

Local Cutaneous Recurrence:

Local cutaneous recurrence after adequate excision of the primary melanoma is associated with aggressive tumor biologic features and is frequently a harbinger of metastases.

Regional Lymphatic and Nodal Recurrences:

The neoplastic nature of the regional recurrences should be attempted and confirmed by histology/cytology.

- In Transit Metastases: In transit metastases represents the clinical manifestations of small tumor emboli trapped within the dermis and subdermal lymphatics between the site of the primary tumor and the regional lymph node drainage basin(s). In extremities, in transit metastases can also occur distal to the site of the primary lesion as a result of reversed lymphatic flow. In transit metastases occur in 10% to 15% in patients with Stage III disease. Although previous staging systems distinguished between the small satellitosis (within 2 cm of the primary tumor), pathophysiologically these two events represent different points on a continuum of the same biologic process. When present, in transit metastases are usually multiple, evolve over time, and, as previously stated, are often the harbinger of subsequent systemic disease.
- Regional Node Recurrences: Regional node failure in a previously dissected basin is usually found at the periphery of the prior surgical procedure.

Patterns of Metastases:

Melanoma is well known for its ability to metastasize to virtually any organ or tissue. The most common initial sites of distance metastases are the non-visceral (skin, subcutaneous tissue, and lymph nodes), which are recurrence sites for 42% to 59% of subjects in various studies. Visceral locations are the lung, brain, liver, gastrointestinal tract, and bone; the visceral sites are the initial sites of relapse in approximately 25% of all melanoma patients who experience recurrence.

Measurable Disease per RECIST 1.1:

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

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

Malignant lymph nodes: to be considered pathologically enlarged and measurable per RECIST 1.1, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm).

If the measurable disease is restricted to a solitary lesion (visceral or nodal), its neoplastic nature must be confirmed either by cytology/histology or by lesion progression certified on the next CT/MRI examination.

Nonmeasurable Disease per RECIST 1.1:

Nonmeasurable lesions include all other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 and < 15 mm short axis), as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include: leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitic involvement of

skin or lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note:

- Cutaneous relapses occurring beyond the periphery of the previous surgical bed (ie, over 2 cm) are considered distant metastases.
- Node relapses occurring beyond the anatomical compartment of the dissected basins are considered distant metastases.
- Node relapses in nodal basins situated in a different anatomical compartment or beyond the previously dissected basin or in two nodal basins (even if contiguous; ie, 2 pelvic nodal basines, 2 mediastinal nodal basins) are considered distant metastases.

5.4.2 Methods of measurements

- CT and MRI are an essential part of the work-up to establish recurrence. Conventional CT with IV contrast and MRI gadolinium should be performed with contiguous cuts of 10 mm or less slice thickness. Spiral CT should be performed using a 3- or 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen and pelvis while head & neck tumors and those of the extremities usually require specific protocols. In each institute the same technique for CT/MRI should be used to characterize each new lesion.
  - For subjects allergic to contrast media, they may have a CT performed without contrast after discussion and agreement with the medical monitor
- PET alone will not be considered for the disease assessment. Complementary CT and/or MRI or biopsy must be performed in such cases.
- Cytology and/or histology are mandatory to confirm recurrence in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions. Histological or cytological evidence of recurrence should be attempted in all cases except for brain metastases when safe and clinically feasible. An example when obtaining a biopsy to confirm recurrence may not be safe and clinically feasible is brain metastases.
- Clinically detected new lesions:
  - Superficial cutaneous lesions: the neoplastic nature must be confirmed by cytology/histology.
  - Deep subcutaneous lesions and lymph node lesions should be documented by ultrasound and histological/cytological evidence should be attempted. In absence of pathology report, lesion recurrence will be documented with a CT scan/MRI.
- Tumor markers or auto-antibodies alone cannot be used to assess recurrence.

5.4.3 Date of Recurrence

The first date when recurrence was observed is taken into account regardless the method of assessment. Therefore recurrence will be declared for any lesion when:

- Only imaging was performed and recurrence confirmed

- Only pathology was done and malignancy confirmed (in solitary or in doubtful lesions, cutaneous, subcutaneous or lymph node lesions)
- Both pathology and imaging were done and recurrence/malignancy confirmed. In this case, the date of whichever examination comes first is considered the date of recurrence.

Pathology reports of biopsies confirming recurrence should be sent to a central vendor.

Note: for documentation, the date of recurrence is the date that the pathology and/or imaging confirms recurrence--not the date that the information was communicated to the subject.

[redacted]

[redacted]

5.7 Outcomes Research Assessments

HRQoL will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is the most commonly used QoL instrument in melanoma clinical studies. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 comprises 5 functional scales (physical functioning, cognitive functioning, emotional functioning, social functioning and global quality of life) as well as nine symptom scales (fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Except for the overall health status and global quality of life items, responses for all items are 4 point categorical scales ranging from 1 (Not at all) to 4 (Very much). The overall health status/quality of life responses are 7-point Likert scales.

[redacted]

[redacted]

All PRO instruments will be administered during on-study, and follow-up phases as outlined in Table 5.1-2, Table 5.1-3, Table 5.1-4, Table 5.1-5, Table 5.1-6, and Table 5.1-7, respectively, to all randomized subjects.

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

As of Revised Protocol 06, collection of EQ-5D-3L is not required during extended survival follow-up. Additional sample collection is unlikely to change interpretation of biomarker data that have already been analyzed.

[redacted]

[redacted]

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

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

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

hospitalization.) Potential drug induced liver injury (DILI) is also considered an important medical event. (See Section 6.6 for the definition of potential DILI.)

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

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

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

NOTE:

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

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

6.1.1 Serious Adverse Event Collection and Reporting

Sections 5.6.1 and 5.6.2 in the Investigator Brochure (IB) represent the Reference Safety Information to determine expectedness of serious adverse events for expedited reporting. Following the subject's or the legal representative'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. Subjects who are randomized and never treated with study drug, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg. a follow-up skin biopsy).

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

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

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

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS (or designee) within 24 hours 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. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

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

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 6.1.1). Follow-up is also required for nonserious AEs that cause withholding 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. Every adverse event must be assessed by the investigator with regards to whether it is considered immune mediated. For events which are potentially immune mediated, additional information will be collected on the subject's case report form.

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 omitted or discontinued
- 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

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

The investigator must immediately notify the BMS (or designee) Medical Monitor of this event and complete and forward a Pregnancy Surveillance Form to BMS (or designee) within 24 hours 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:

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee (DMC) will be established to provide oversight of safety and efficacy considerations in protocol CA209238. Additionally, the DMC will provide advice to the sponsor regarding actions the committee deems necessary for the continuing protection of subjects enrolled in the study. The DMC will be charged with assessing such actions in light of an acceptable benefit/risk profile for nivolumab and ipilimumab. The DMC will act in an advisory capacity to BMS and will monitor subject safety and evaluate the available efficacy data for the study. The oncology therapeutic area of BMS has primary responsibility for design and conduct of the study.

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

The final DMC meeting occurred on 28-Apr-2020.

8 STATISTICAL CONSIDERATIONS

As of Revised Protocol 06, all planned analyses were conducted based on the 48-month minimum follow-up database lock, which occurred in Jan-2020. No additional formal efficacy analyses will be conducted for newly collected efficacy data. Exploratory analysis on these new efficacy data will be conducted using similar analyses described in the Clinical Study Report (CSR) Statistical Analysis Plan (SAP) for the 48-month minimum follow-up database lock. Exploratory analyses will be performed, eg, every other year, though the analysis schedule might be adjusted based on the additional number of events accumulated.

8.1 Sample Size Determination

The sample size is calculated to compare RFS between subjects randomized to receive nivolumab vs ipilimumab. RFS will be evaluated for a treatment effect at an overall alpha level of 0.05 (two-sided) with approximately 85% power. The number of events and power were calculated assuming a delayed treatment effect and cure fraction.

Approximately 900 subjects have been randomized to the two treatment arms in a 1:1 ratio. Based on current accrual and revised piece-wise accrual rate assumptions, accrual duration was 7.5 months. Taking into account the actual AJCC disease stage distribution, slower event rate, higher cure rates, and some early drop-out, the original planned 507 events might not be reached by the final RFS analysis (ie, after all subjects have a minimum of 36 months of follow-up). Approximately 450 RFS events are anticipated at the final RFS analysis, ensuring at least 85% power to detect a hazard ratio of 0.75 (critical hazard ratio of 0.83) with an overall type I error of 0.05 (two-sided). Sample size calculations for this study design were done using EAST 6 (v 6.3.1) and R.

An interim analysis of RFS will take place after all subjects have a minimum of 18 months of follow-up. Approximately 350 RFS events are anticipated at this analysis. The stopping boundary at the interim analysis will be derived based on the exact number of RFS events at interim using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. With an interim RFS analysis at 350 RFS events (about 78% information fraction), the critical hazard ratio would be 0.78 and the type I error would be 0.022 (two-sided). The type I error to be used for final RFS analysis would be 0.043 (two-sided).

8.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS.
- All randomized subjects: All subjects who were randomized to any treatment arm in the study.
- All treated subjects: All subjects who received any study drug nivolumab or ipilimumab including placebo doses.

[redacted]

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary endpoint is RFS. The primary endpoint of RFS will be programmatically determined based on the disease recurrence date provided by the investigator and is defined as the time between the date of randomization and the date of first recurrence (local, regional or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. (Note: a subject who dies without reported recurrence will be considered to have recurred on the date of death.) For subjects who remain alive and whose disease has not recurred, RFS will be censored on the date of last evaluable disease assessment. For those subjects who remained alive and had no recorded post-randomization tumor assessment, RFS will be censored on the day of randomization. Censoring rules for the primary analysis of RFS are presented in Table 8.3.1-1.

Table 8.3.1-1: Censoring Scheme for Primary Definition of RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date of last evaluable disease assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without recurrence reported prior to or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of initiation of subsequent therapy	Censored
Second non-melanoma primary cancer reported prior or on the same day of disease assessment	Date of last evaluable disease assessment prior to or on the same date of diagnosis of second non-melanoma primary cancer	Censored

RFS, recurrence-free survival

As of Revised Protocol 06, since no study-specified surveillance assessments are to be collected beyond Year 5, the censoring rules for defining RFS will be different from the primary definition above. RFS will be defined as the time between the date of randomization and the date of first recurrence (local, regional, or distant metastasis), new primary melanoma, or death (whatever the cause), whichever occurs first. (Note: A subject who dies without reported recurrence will be considered to have recurred on the date of death.) For subjects who remain alive and whose disease has not recurred, RFS will be censored on the last date the subject was known to be alive. Censoring rules for the exploratory analysis of RFS are presented in Table 8.3.1-2.

Table 8.3.1-2: Censoring Scheme for Definition of RFS

Situation	Date of Event or Censoring	Outcome
Recurrence (local, regional, distant, new primary melanoma)	Date of first recurrence	Event
Death without recurrence	Date of death	Event
Disease at baseline	Date of randomization	Event
No baseline disease assessment	Date of randomization	Censored
No on-study disease assessments and no death	Date of randomization	Censored
No recurrence and no death	Date last known to be alive	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received	Date of initiation of subsequent therapy	Censored

Table 8.3.1-2: Censoring Scheme for Definition of RFS

Situation	Date of Event or Censoring	Outcome
without recurrence reported prior to or on the same day of disease assessment		
Second non-melanoma primary cancer reported prior or on the same day of disease assessment	Date of diagnosis of second non-melanoma primary cancer	Censored

RFS, recurrence-free survival

8.3.2 Secondary Endpoint(s)

The first secondary endpoint (OS) is defined as the time between the date of randomization and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

The second secondary endpoint (to assess the safety and tolerability of nivolumab and ipilimumab) will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

The third secondary endpoint (to evaluate PD-L1 expression as a predictive biomarker) will be measured by the endpoint RFS based on PD-L1 expression level.

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

[redacted]

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment arm as randomized using descriptive statistics for all randomized subjects.

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

The primary RFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status and Stage at screening in randomized subjects. The hazard ratio and corresponding two-sided (1-adjusted α)% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. RFS curves, RFS medians with 95% CIs, and RFS rates at 6, 12, 18, 24 and 36 months with 95% CIs will be estimated using Kaplan-Meier methodology.

8.4.2.2 Secondary Endpoint Methods

The secondary OS analysis will be conducted using a two-sided log-rank test stratified by PD-L1 status and Stage at screening in randomized subjects. The hazard ratio and corresponding two-sided (1-adjusted α)% CI will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs and OS rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

To evaluate PD-L1 expression as a predictive biomarker, a Cox proportional hazards model will be used to test the interaction between PD-L1 expression (positive vs negative) and treatment arm for the RFS endpoint. Additionally, RFS will be analyzed within each PD-L1 expression subgroup (positive and negative) including log-rank tests and hazard ratios with corresponding confidence intervals. RFS curves and medians will be estimated using Kaplan-Meier methodology. These analyses will be descriptive and not adjusted for multiplicity. Other exploratory analyses, such as associations between PD-L1 expression and other efficacy endpoints and evaluations of different thresholds for PD-L1 positivity, will also be planned in the SAP.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using NCI CTCAE version 4.0 by treatment group. All on-study AEs, treatment-related AEs, SAEs, and treatment-related SAEs will be tabulated using worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, chemistry, liver function, and renal function will be summarized using worst grade NCI CTCAE v 4.0 criteria.

[redacted]

[redacted]

8.4.6 Outcomes Research Analyses

EORTC QLQ C-30

The analysis of EORTC QLQ C-30 will be performed in all randomized who have an assessment at baseline and at least one follow-up assessment.

All scales and single items are scored on a categorical scales and linearly transformed to 0-to-100 scales with higher scores for a functional scale representing higher levels of functioning, higher scores for the global health status/quality of life representing higher levels of global health status/quality of life and higher scores for a symptom scale representing higher level of symptoms.

EORTC QLQ C-30 global health status/QoL composite scale data and the remaining EORTC QLQ C-30 scale data will be summarized by timepoint using descriptive statistics for each treatment arm. Exploratory analyses may be performed to examine differences between the 2 arms.

[redacted]

8.5 Interim Analyses and Hierarchical Testing

An interim analysis of RFS will be conducted after all subjects have a minimum of 18 months of follow-up. Approximately 350 RFS events are anticipated at this analysis. The stopping boundaries at the interim and final analyses will be derived based on the exact number of RFS events using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. No interim analysis of OS will be performed at this time

If RFS is significant, the trial will continue and OS will be tested hierarchically. One formal OS interim analysis will be conducted at the time of the final RFS analysis. This formal comparison of OS will allow for early stopping for superiority. The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries.

The final OS analysis will take place after all subjects have a minimum of 48 months of follow-up, which will take place approximately 55.5 months from the start of the study. At the time of the final OS analysis, 302 events are expected ensuring approximately 88% overall power to detect a hazard ratio of 0.70. Details of the OS modeling will be presented in the SAP.

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

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

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

9.1.2.1 Source Documentation

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (inventoried and dispensed) is maintained at the study site. 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 CSR.

For this protocol, the Signatory Investigator will be selected as appropriate based on the following criteria:

- Subject recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Other criteria (as determined by the study team).

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

10 GLOSSARY OF TERMS

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

11 LIST OF ABBREVIATIONS

Term	Definition
ADA	anti-drug antibody
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT	aminotransaminases
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
HCG	human chorionic gonadotrophin
BMS	Bristol Myers Squibb
BP	blood pressure
BUN	blood urea nitrogen
CBC	complete blood count
CI	confidence interval
CL	clearance
cm	centimeter
Cmax	maximum observed concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	Complete response
CRF	Case Report Form, paper or electronic
CSR	clinical study report
CT	computed tomography
CTA	Clinical trial agreement
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T lymphocyte associated antigen-4
DILI	drug-induced liver injury
dL	deciliter
DLT	dose limiting toxicity

Term	Definition
DMC	data monitoring committee
DMFS	distant metastases-free survival
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFS	Event-free survival
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
EORTC	European Organization for Research and Treatment of Cancer
EDC	Electronic Data Capture
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	heart rate or hazard ratio
HRQoL	Health Related Quality of Life
HRT	hormone replacement therapy
IB	Investigator Brochure
irAE	immune-related adverse event
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IHC	immunohistochemistry
IMP	investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
ITSM	immunoreceptor tyrosine-based switch motif
IU	International Unit
IV	intravenous
IVRS	Interactive Voice Response System

Term	Definition
kg	kilogram
L	liter
LDH	lactate dehydrogenase
LFT	liver function test
MDSC	Myeloid derived suppressor cells
mg	milligram
mL	milliliter
MLR	mixed lymphocyte reaction
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
MU	million units
µg	microgram
N	number of subjects or observations
N/A	not applicable
NSCLC	non-small cell lung cancer
NED	no evidence of disease
ng	nanogram
NIMP	non-investigational medicinal products
Obs.	Observation
ORR	Objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD-1	programmed death receptor-1
PFS	Progression free survival
PK	pharmacokinetics
PPK	Population pharmacokinetic
PR	Partial response
PRO	Patient Reported Outcome
QoL	Quality of Life
QLQ-C30	Quality of Life Questionnaire-Core

Term	Definition
RCC	renal cell carcinoma
RFS	recurrence free survival
RT	radiation therapy
TCR	T-cell receptor
SAE	serious adverse event
SAP	Statistical Analysis Plan
SNP	single nucleotide polymorphism
T-HALF	Half life
Tmax	time of maximum observed concentration
ULN	upper limit of normal
US	United States
VAS	visual analog rating scale
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
WBC	white blood cell
WOCBP	women of childbearing potential
WPAI:GH	Work Productivity and Activity Impairment : General Health