Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535-46. DOI: 10.1056/NEJMoa1910836

Study CA209-067

This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan, final statistical analysis plan, summary of changes.

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Clinical Protocol CA209067

A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma.

(CheckMate 067: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 067)

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Original Protocol	19-Mar-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209067

Protocol Title:

A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma. (CheckMate 067: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 067)

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

- Nivolumab (BMS-936558) monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or
- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3mg/kg every 2 weeks until progression or
- Ipilimumab monotherapy administered IV over 90 minutes at 3 mg/kg every 3 weeks for a total of 4 doses

Study Phase: 3

Research Hypothesis: Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve overall survival compared to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma.

Objectives:

Primary Objective:

- To compare the overall survival (OS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma

Secondary Objectives:

- To compare Progression Free Survival (PFS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To compare Objective Response Rate (ORR) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with advanced melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for OS.
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Care (EORTC) QLQ-C30

Exploratory Objectives:

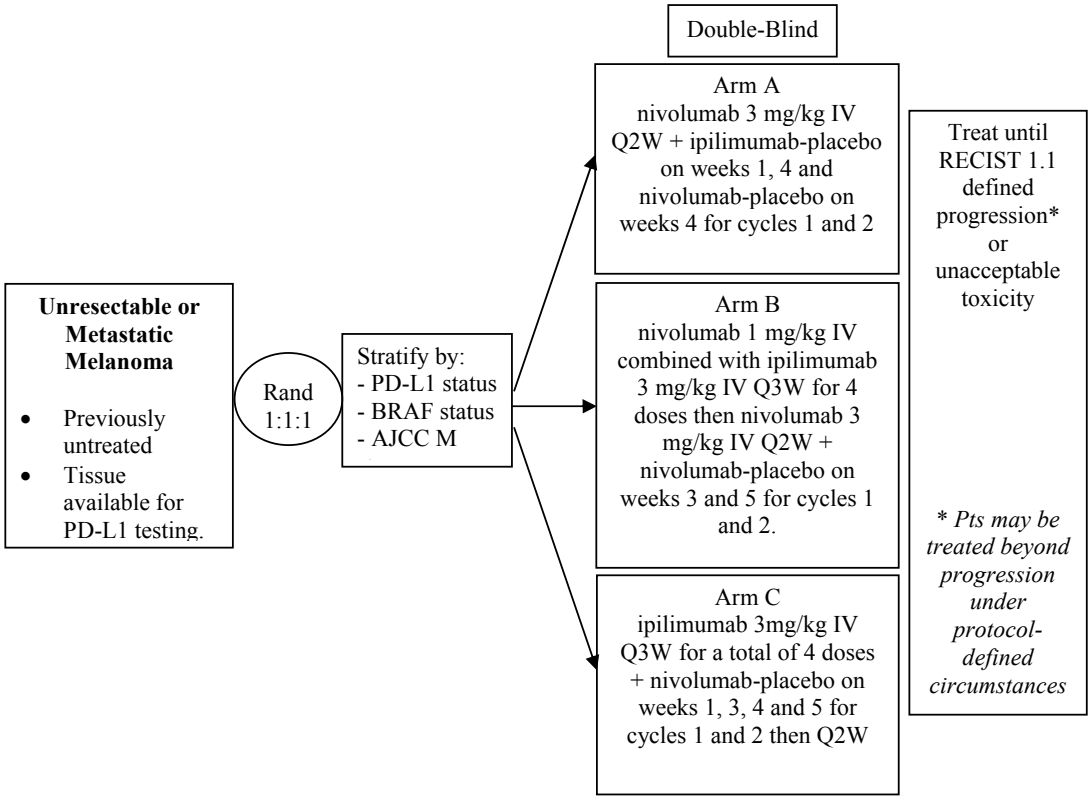
Exploratory objectives are listed in Section 1.3.3 of the protocol.

Study Design:

This is a Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated unresectable or metastatic melanoma. Subjects must have stage III (unresectable) or stage IV melanoma, as per the American Joint Committee on Cancer (AJCC) staging system, and must not have received prior therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization. Subjects will be randomized 1:1:1 and stratified by PD-L1 status (positive vs. negative/indeterminate), BRAF Status (BRAF mutation positive, BRAF wildtype), and AJCC M stage (M0/M1a/M1b vs. M1c). One cycle of treatment is defined as six weeks. Subjects will be treated with one of the following:

- Arm A: nivolumab 3 mg/kg IV Q2W + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2.
- Arm C: ipilimumab 3mg/kg IV Q3W for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then Q2W

For Arm B, the dose/schedule will be finalized in the protocol and rationale supported by CA209004 (A Phase 1b, Open-Label, Multicenter, Multidose, Dose-Escalation Study of MDX-1106 (BMS-936558)(Nivolumab) in Combination with Ipilimumab (BMS-734016) in Subjects with Unresectable Stage III or Stage IV Malignant Melanoma). One cycle of treatment will be defined as six weeks. Dose reductions will be not be allowed.



Study Population:

Key Inclusion Criteria:

- ECOG PS 0 or 1.
- Histologically confirmed stage III (unresectable) or stage IV melanoma, as per AJCC staging system.
- Treatment naïve patients (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted. Note that prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized.
- Measurable disease by CT or MRI per RECIST 1.1 criteria.
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.
- Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period

Key Exclusion Criteria:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Ocular melanoma.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

Study Assessments:

Overall survival is the primary endpoint of the study. Subjects will be assessed for response by CT or MRI beginning at 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for the first year and then every 12 weeks (± 1 week) until progression or treatment discontinuation, whichever occurs later. Overall survival is defined as the time from randomization to the date of death.

Statistical Considerations:

Sample Size:
The sample size is calculated to compare OS between nivolumab and ipilimumab and to compare OS between ipilimumab combined with nivolumab and ipilimumab at a Type I error level of 0.025 (two-sided) for each comparison. Hochberg's procedure[57] will be applied to control the overall Type I error at an alpha of 0.05 (two-sided). The number of events and power are calculated assuming an exponential distribution in each treatment group. No interim analysis will be performed.

Approximately 915 subjects will be randomized to the three treatment groups in a 1:1:1 ratio. For each OS comparison, at least 460 events in the two respective treatment groups provide at least 90% power to detect a hazard ratio (HR) of 0.72 with a type I error of 0.025 (two-sided). The HR of 0.72 corresponds to a 39% increase in the median OS, assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment groups. Assuming the distribution of events follows the alternative hypothesis, approximately 247 events in the control group and 213 in each of the experimental groups are expected.

In time-to-event trials, the final analysis typically occurs when a certain number of events, pooled across treatment groups, are observed such that the trial is adequately powered under the design assumptions. However, in the previously untreated unresectable and metastatic melanoma ipilimumab trial, CA184024, the projected trial duration of 34 months was very different from the actual trial duration of 54 months, with the event rate slowing dramatically in the last 18 months. In order that such a phenomenon does not unduly delay the final analysis in the current trial, the analysis of both primary OS comparisons will be conducted when approximately 247 events (ie, deaths) in the control group have been observed. This approach has the added effect of harmonizing the timing of the two comparisons. An external statistical group will be utilized to track the number of events in the control group and alert the sponsor when the required number of events has been observed for final analysis.

Endpoints:

Primary Endpoint:

OS is the primary endpoint for this study.

Secondary Endpoints:

If OS superiority is demonstrated for either comparison, a gatekeeping testing approach for the key secondary endpoints will be applied to additional experimental vs. control comparisons as described in the statistical analysis plan. Key secondary endpoints include PFS and ORR.

Analyses:

Each of the two primary OS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in all randomized subjects using Hochberg's procedure[57] to address multiplicity. Hazard ratios (HR) and corresponding two-sided (1-adjusted α)% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment group 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.

PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided (1-adjusted α)% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage to compare each of the two experimental treatments to the control group. Associated odds ratios and (1-adjusted α)% CI will also be calculated. Additionally, ORRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment groups.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental groups, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

The totality of OS results will be summarized in a single graphical display that includes Kaplan-Meier curves for the three treatment groups, the log-rank p-values for the two formal comparisons, the three HRs and corresponding CIs, and the three KM medians and corresponding CIs. PFS results will be summarized similarly.

Descriptive analyses will be performed to evaluate the potential of PD-L1 expression as a predictive biomarker for OS.

EORTC QLQ C-30 global health status/QoL composite scale data and the remaining EORTC QLQ C-30 scale data will be summarized by time point using descriptive statistics for each treatment group.

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2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles

underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives 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.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or

metastatic Stage III or stage IV melanoma, as per the AJCC staging system, and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization.

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

- PD-L1 status
    - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
    - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- BRAF status
    - BRAF mutation positive vs
    - BRAF wildtype
- AJCC M stage (See Appendix 3)
    - M0/M1a/M1b vs
    - M1c

Subjects will be treated in a blinded fashion with one of the following:

- Arm A: nivolumab 3 mg/kg IV Q2W + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2.
- Arm C: ipilimumab 3 mg/kg IV Q3W for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then Q2W

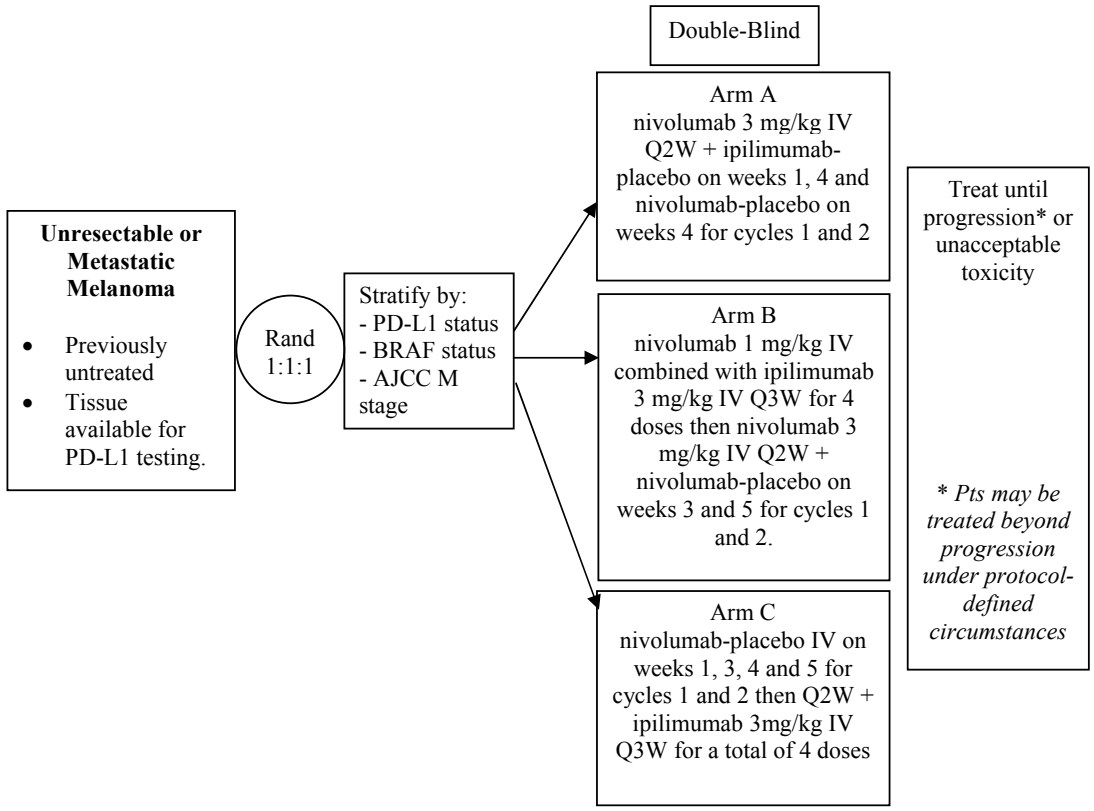
Depending on the treatment arm, the subject will receive a placebo; nivolumab-placebo or ipilimumab-placebo that closely matches either nivolumab or ipilimumab, respectively. The placebos are administered as per the dosing guidelines of the matching drug. The schedule of placebo administration will depend on the treatment arm. See Table 4.3-1 and Table 4.3-2

One cycle of treatment will be defined as six weeks. Dose reductions will be not be allowed for any of the treatments. On-study tumor assessments will begin 12 weeks from randomization and will continue every 6 weeks for the first year and every 12 weeks thereafter until disease

progression or treatment discontinuation, whichever occurs later. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating study drug.

The study design schematic is presented in Figure 3.1-1

Figure 3.1-1: Study Design Schematic



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

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase,

subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses

Treatment Phase:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to either the nivolumab + placebo arm (Arm A), the nivolumab + ipilimumab arm (Arm B) or the ipilimumab + placebo arm (Arm C).
- A negative pregnancy test should be documented within 24 hours prior to the start of investigational product.
- PRO (Patient Reported Outcome) instruments must be completed after randomization, prior to the first dose of study therapy and according to the schedule in Table 5.1-2.
- Within 3 days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1).
- On-study laboratory assessments (Cycle 2 and beyond) should be drawn within 72 hours prior to dosing.
- Adverse event assessments should be documented at each clinic visit. WOCBP must have a pregnancy test during week 1 and week 4 for cycles 1-2 and week 1 and week 5 of starting from cycle 3. Table 5.1-2 and Table 5.1-3
- PK samples and immunogenicity samples will be collected according to the schedule in Table 5.5-1
- Study drug dosing may be delayed for toxicity. See Section 4.3.2

For the first 2 cycles (12 weeks);

- In subjects on the nivolumab + placebo arm (Arm A), nivolumab is administered every 2 weeks for 6 doses + placebo Table 4.3-1
- In subjects on the nivolumab combined with ipilimumab arm (Arm B), nivolumab and ipilimumab are administered every 3 weeks for 4 doses + placebo Table 4.3-1
- In subjects on the ipilimumab + placebo arm (Arm C), ipilimumab is administered every 3 weeks for 4 doses + placebo Table 4.3-1

Starting cycle 3;

- In subjects on the nivolumab + placebo arm (Arm A), nivolumab is administered every 2 weeks Table 4.3-2
- In subjects on the nivolumab combined with ipilimumab arm (Arm B), nivolumab is administered every 2 weeks Table 4.3-2
- In subjects on the ipilimumab + placebo arm (Arm C), placebo is administered every 2 weeks Table 4.3-2
- Study drug dose may be delayed for toxicity. See Section 4.3.2

- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for the first 12 months, and then every 12 weeks (± 1 week) until disease progression or treatment discontinuation, whichever occurs later.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5.

Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Two follow-up visits include collection of PK/immunogenicity samples Table 5.5-1.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 12 weeks (±1week) after randomization and continuing every 6 weeks (±1 week) for the first 12 months from randomization, and every 12 weeks (±1 week) thereafter until documented tumor progression.
- Subject's treatment assignment will be unblinded to the site for those subjects who have disease progression **and** have discontinued treatment.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.
- PRO instruments will be completed according to the schedule in Table 5.1-4.

The total duration of the study from start of randomization to final analysis of OS is expected to be 44.1 months (17 months of accrual + 27.1 months of follow-up), assuming a piecewise accrual rate (3 subjects during Month 1, 6 subjects during Month 2, 27 subjects/month during Months 3 to 4, 48 subjects/month during Months 5 to 6, 69 subjects/month after Month 6). Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

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

2. Target Population

a) Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system.

b) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (Refer to Appendix 2)

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

d) Measurable disease by CT or MRI per RECIST 1.1 criteria.5.4.3.1

e) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.

f) Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period

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

h) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:

i) WBC ≥ 2000/μL

ii) Neutrophils ≥ 1500/μL

iii) Platelets ≥ 100 x10^3/μL

iv) Hemoglobin > 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

vi) AST/ALT ≤ 3 x ULN

vii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can 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 pre-treatment failure (ie, subject has not been randomized / has not been treated) after obtaining agreement from the medical monitor prior to re-enrolling a subject. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Men and women, ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in Appendix 5. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives. The half-life of BMS- 936558 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 23 weeks (30 days plus the time required for nivolumab to undergo five half lives) after the last dose of investigational drug.

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

d) Women must not be breastfeeding

e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half lives. The half-life of nivolumab and ipilimumab is up to 25 days and 18 days, respectively. Given the blinded nature of the study, men who are sexually active with WOCBP must continue contraception for 31 weeks (90 days plus the time required for nivolumab to undergo five half lives) after the last dose of investigational drug.

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

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

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

b) Ocular melanoma

2. Medical History and Concurrent Diseases

a) Any participation in a Phase 3 ipilimumab trial

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

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

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

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

f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) 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 allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

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

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes. In additional, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.4 or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in Section 3.4.2.1, or standard or investigational agents for treatment of cancer).

Supportive care for disease-related symptoms may be offered to all subjects on the trial

3.4.2 Other Restrictions and Precautions

3.4.2.1 Palliative Radiation Therapy

Palliative (limited-field) radiation therapy is permitted, but only for pain control to sites of bone disease present at baseline and only if all of the following criteria are met:

1. Repeat imaging demonstrates no new sites of bone metastases.
2. The lesion being considered for palliative radiation is not a target lesion.
3. The case is discussed with the BMS medical monitor, and the medical monitor agrees that the conditions required to receive palliative radiation are met.

3.4.3 Surgical Resection Following initial Response

Investigators may choose to resect solitary lesions in patients with unresectable or metastatic melanoma and render the patient free of macroscopic disease. Subjects enrolled in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 18 re-staging assessments. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment (eg, Week 18), it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Patients with a PR who go on to have surgical resection of remaining disease will be considered a PR. Tumor tissue of any resected solitary lesion should be submitted to BMS (see section 5.6.1.) Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of these specimens will be provided in a separate Procedure Manual at the time of study initiation.

3.4.4 Permitted Therapy

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

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects from Treatment

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

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

- Additional protocol specified reasons for discontinuation (see Section 4.3.5)

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

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

3.6 Post Treatment Study Follow up

In this study, overall survival is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 Study Assessments and Procedures until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

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

information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

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

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

4.1 Study Treatments

Table 4.1-1: Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

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

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 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.

4.1.1 Investigational Product

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

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

In this protocol, investigational product(s) is/are: BMS-936558 (nivolumab), ipilimumab, nivolumab-placebo (0.9% Sodium Chloride Injection) and ipilimumab-placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection).

4.1.2 Non-investigational Product

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

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

4.1.3 Handling and Dispensing

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

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

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

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab.

Nivolumab (BMS-936558)

Nivolumab (BMS-936558) vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab or Nivolumab-Placebo is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing,gloves, and safety cabinets.

The same storage and use conditions recommended for product also apply to the placebo for Ipilimumab Injection.

Ipilimumab or Ipilimumab-Placebo is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

4.2 Method of Assigning Subject Identification

CA209067 (CheckMate 067) is a randomized, double-blind study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

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

- Subject number
- Date of birth
- PD-L1 status (PD-L1 positive vs. PD-L1 negative/indeterminate) entered by vendor
- BRAF status
- M Stage (see Appendix 3)

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

- PD-L1 status
  - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)

- M Stage (see Appendix 3)
  - M0/M1a/M1b vs
  - M1c

- BRAF status
  - Wild type vs
  - Mutation positive

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

4.3 Selection and Timing of Dose for Each Subject

Dosing schedule for all three arms is detailed in Table 4.3-1 and Table 4.3-2.

Table 4.3-1: Dosing Schedule for Cycle 1 and Cycle 2

1 Cycle = 6 weeks						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
Arm A (Nivolumab Monotherapy 3mg/kg + Placebo)	3mg/kg Nivolumab 3 mg/kg Ipilimumab-Placebo		3 mg/kg Nivolumab	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	
Arm B (Nivolumab 1mg/kg + Ipilimumab 3 mg/kg)	1 mg/kg Nivolumab [a] 3 mg/kg Ipilimumab		3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab[a,] 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	
Arm C (Ipilimumab Monotherapy 3mg/kg+ Placebo)	3 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab		3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	

[a] Arm B - In order to protect the blind, the 1mg/kg nivolumab administered on D1W1 and D1W4 in cycles 1 and 2 should be diluted to the same volume as 3 mg/kg nivolumab-placebo prepared on D1W3 and D1W5

Table 4.3-2: Dosing Schedule Cycle 3 and Beyond

1 Cycle = 6 weeks						
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6
Arm A (Nivolumab Monotherapy + Placebo)	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	
Arm B (Nivolumab + Ipilimumab)	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	
Arm C (Ipilimumab Monotherapy + Placebo)	3 mg/kg Nivolumab-Placebo		3 mg/kg Nivolumab-Placebo		3 mg/kg Nivolumab-Placebo	

First dose to be administered within 3 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 nivo-placebo infusion.

Ipilimumab or ipilimumab-placebo may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab or nivolumab-placebo may be diluted in 0.9% Sodium Chloride Solution.

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose modifications allowed.

During cycles 1 and 2

- subjects may be dosed no less than 12 days between
  - C1W1 and C1W3
  - C1W5 and C2W1
  - C2W1 and C2W3
- subjects may be dosed no less than 5 days between
  - C1W3 and C1W4
  - C1W4 and C1W5
  - C2W3 and C2W4
  - C2W4 and C2W5

Starting from cycle 3, subjects may be dosed no less than 12 days from the previous dose of drug.

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

4.3.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See section 4.3.6 for premedication recommendations following a nivolumab or ipilimumab related infusion reaction.

4.3.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume (see Section 4.3.4.)

Dose delay criteria also apply for the placebo version of each agent, given the blinded nature of this study.

Nivolumab and ipilimumab administration should be delayed for the following:

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

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and nephrotoxicity.

Given blinded nature of the study and in order to standardize the management across all three arms, for the overlapping adverse event management algorithms present in both the BMS-936558 (nivolumab) and ipilimumab IB (**GI, hepatic, and endocrine** algorithms), the recommendations are to follow the BMS-936558 (nivolumab) IB adverse event algorithms as opposed to the ipilimumab IB algorithms.

Therefore, the algorithms recommended for utilization in CA209-067 are included in Appendix 4.

4.3.3 Dose Modifications

Dose reductions or dose escalations are not permitted.

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

4.3.4 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 delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5)should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

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

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.

4.3.5 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 the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for 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

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
  - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
  - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

4.3.6 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 NCI CTCAE (version 4.0) guidelines.

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

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

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

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal

anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours).

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

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

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.3.7 Treatment Beyond Disease Progression

As described in Section 1.5 accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[56]

Subjects will be permitted to continue Arm A, B, or C treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit
  and
- Subject is tolerating study drug.

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

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

Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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

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

4.4 Blinding/Unblinding

During the blinded portion of the study, blinding of treatment assignment is critical to the integrity of this clinical study. 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 during the blinded portion of the study. The subject’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded during the blinded portion of the study.

Before breaking the blind of an individual subject's treatment during the blinded portion of the study, 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 during the blinded portion of the study be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind

during the blinded portion of the study. The Principal Investigator should only call for emergency unblinding during the blinded portion of the study AFTER the decision to discontinue the subject has been made.

For subjects who are receiving treatment and have not progressed, the Sponsor, subjects, investigator and site staff will be blinded to the study drug administered (nivolumab + placebo or ipilimumab + placebo or nivolumab plus ipilimumab). Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to provide oversight of drug supply and other unblinded study documentation. Upon progression of disease and treatment discontinuation of each subject, the investigator and subject will be unblinded to each subject's treatment assignment through the IVRS. The Sponsor's central protocol team (including but not limited to clinical, statistics, data management) will remain blinded.

For this study, the method of unblinding is through the IVRS.

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

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

Any request to unblind a subject for non-emergency purposes during the blinded portion of the study should be discussed with the Medical Monitor.

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

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, ie, incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

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

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

4.6.2 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209067)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Medical History	X	
Tumor Tissue Samples	X	Sufficient tumor tissue from an unresectable or metastatic site (block or minimum of 10 slides; obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen).
Safety Assessments		
Physical Examination	X	
Vital Signs and oxygen saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion. Obtain vital signs at the screening visit and within 72 hours prior to first dose
Physical Measurements (including performance status)	X	Height and weight
ECG	X	Within 14 days prior to randomization
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication Collection	X	Within 14 days prior to randomization
Laboratory Tests	X	CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C(HBV sAG, HCV antibody), within 14 days prior to randomization
Pregnancy Test (WOCBP Only)	X	

Table 5.1-1: Screening Assessments (CA209067)		
Procedure	**Screening Visit**	**Notes**
Efficacy Assessment		
Screening/Baseline Tumor Assessments	X	Chest, Abdomen, Pelvis and Brain and all other known sites of disease within 28 days prior to randomization

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Safety Assessments							
Targeted Physical Examination	X		X	X	X		To be performed only as clinically indicated.
Vital Signs and Oxygen Saturation	X		X	X	X		Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing.
Physical Measurements (including performance status)	X		X	X	X		Weight and ECOG status
Adverse Events Assessment	Continuously						
Review of Concomitant Medications	X		X	X	X		
Laboratory Tests	X			X			Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, 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 (WOCBP Only)	X			X			Within 24 hours prior to administration of study drug. Serum or Urine
Immunogenicity blood sample	See Table 5.5-1 for details regarding specific sample timing						
Pharmacokinetic Samples							
PK samples	See Table 5.5-1 for details regarding specific sample timing						
Exploratory Biomarker Testing							
Exploratory Serum Biomarkers	X		Y				To be collected pre-dose; Y= only for Cycle 1
Peripheral Blood RNA	X		Y				To be collected pre-dose; Y= only for Cycle 1

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Peripheral Blood Mononuclear Cells (PBMCs)	X		Y				To be collected pre-dose; Y= only for Cycle 1
Whole Blood Sample (DNA)	Y						EDTA Tubes for DNA. Must be obtained prior to dosing. Y= only for Cycle 1.
Efficacy Assessments							
Tumor Assessments						Y	FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization. SUBSEQUENT tumor assessments should occur every 6 weeks (1± wk) until disease progression. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Y=Cycle 2 only
Clinical Drug Supplies							
IVRS-Randomize	Y						Y=Only for cycle 1
Administer Study Treatment	X		X	X	X		First dose to be administered within 3 days following randomization. See section 4.3
Outcomes Research Assessments							
EORTC QLQ C-30	X				X		D1W1 should be completed after randomization but prior to dosing
EQ-5D	X				X		D1W1 should be completed after randomization but prior to dosing

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
WPAI-GH	X				X		D1W1 should be completed after randomization but prior to dosing
Health Care Resource Utilization			X	X	X		Prior to dosing

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209067)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Safety Assessments							
Targeted Physical Examination	X		X		X		To be performed only if clinically indicated.
Vital Signs and Oxygen Saturation	X		X		X		Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing.
Physical Measurements (including performance status)	X		X		X		Weight and ECOG status
Adverse Events Assessment	Continuously						
Review of Concomitant Medications	X		X		X		
Laboratory Tests	X				X		Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, 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 (WOCBP Only)	X				X		Within 24 hours prior to administration of study drug. Serum or Urine
Immunogenicity blood sample	See Table 5.5-1 for details regarding specific sample timing						

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209067)

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Pharmacokinetic Samples							
PK samples	See Table 5.5-1 for details regarding specific sample timing						
Efficacy Assessments							
Tumor Assessments						X	FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization. SUBSEQUENT tumor assessments should occur every 6 weeks (1± wk) up to week 49, then every 12 weeks until disease progression. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.
Clinical Drug Supplies							
Administer Study Treatment	X		X		X		See section 4.3
Outcomes Research Assessments							
EORTC QLQ C-30	X				Y		Prior to dosing. Y=only during 1st 6 months
EQ-5D	X				Y		Prior to dosing. Y=only during 1st 6 months
WPAI-GH	X				Y		Prior to dosing. Y=only during 1st 6 months
Health Care Resource Utilization	X		X		X		Prior to dosing at every study drug administration visit.

Table 5.1-4: Follow-up Assessments (CA209067) - *All Subjects*

Procedure	Follow-Up[a], Visits 1 and 2	Survival[b], Follow-up Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN, creatinine and TSH for X01, repeat at X02 if study drug related toxicity persists.
Pregnancy Test	X		Serum or urine
Review of Concomitant Medication	X		
Immunogenicity blood sample	X		Refer to Table 5.5-1 for details regarding specific sample timing
Outcomes Research Assessments			
EORTC QLQ C-30	X		Follow-up visits 1 and 2 only (ePRO)
EQ-5D	X	Y	X=entered by patient, Y=Instrument to be entered by site (ePRO) every 3 months for the first 12 months then every 6 months thereafter.
WPAI-GH	X		Follow-up visits 1 and 2 only (ePRO)
Health Care Resource Utilization	X		Follow-up visits 1 and 2 only
Survival Status			
Subject Status	X	X	Every 3 months, may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy

Table 5.1-4: Follow-up Assessments (CA209067) - *All Subjects*

Procedure	Follow-Up[a], Visits 1 and 2	Survival[b], Follow-up Visits	Notes
Efficacy Assessments			
Tumor Assessments	X		Only for subjects without progression on study therapy. FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization SUBSEQUENT tumor assessments should occur every 6 weeks (± 1 wk) thereafter for the first 12 months, then every 12 wks (± 1 wk) until disease progression Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.
Pharmacokinetic Samples			
PK samples	X		See Table 5.5-1 for schedule of assessments

[a] Follow-up visit 1 (FU1) = 30 days from the last dose +/- 7 days or coincide with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 37 days after last dose, Follow-up visit 2 (FU2) = 84 days (+/- 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from FU2

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 interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide

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 within 28 days prior to randomization. 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 (see Section 5.1).

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, and Hep B and C testing (HBV sAg, HCV Ab) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then during Week 1 and Week 4 of cycle 1 and 2, and Week 1 and Week 5 starting from cycle 3 starting randomization during study therapy and at the safety follow up visits.

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

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

On-study weight and ECOG Performance status should be assessed on Day 1 of Weeks 1, 3, 4 and 5 during cycles 1 and 2 (except Cycle 1 Day 1) and Day 1 of Weeks 1, 3 and 5 starting from Cycle 3 and vital signs should be assessed at each on-study visit (except Cycle 1 Day 1). 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 nivolumab blinded infusion 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 of the next cycle 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 on Day 1 of Weeks 1 and 4 for Cycles 1 and 2 and on Day 1 of Weeks 1 and 5 starting from Cycle 3. 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. 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 patient's 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 patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found the nivolumab Investigator's 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 5.1. Baseline assessments should be performed within 28 days prior to the first dose utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 12 weeks (± 1 week) from randomization and continuing every 6 weeks (± 1 week) for the first 12 months from randomization and every 12 weeks

(± 1 week) thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria.

5.4.1 Primary Efficacy Assessment

The primary endpoint is overall survival (OS) in all randomized subjects. See Section 8.3.1 for the definition of OS.

5.4.2 Secondary Efficacy Assessment

Secondary efficacy endpoints of the study include PFS and ORR in all randomized subjects. See Section 8.3.2 for the definitions of PFS and ORR.

5.4.3 Assessment of Overall Tumor Burden and Measurable Disease

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

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows in Sections 5.4.3.1, 5.4.3.2 and 5.4.3.3

5.4.3.1 Measurable Lesions

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

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

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

5.4.3.2 Non-Measurable Lesions

- All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions.
- Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

5.4.3.3 Special Considerations Regarding Lesion Measurability

Bone Lesions

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

Cystic Lesions

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

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

Non-measurable Lesions

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

5.4.4 Specifications by Method of Measurement

5.4.4.1 Measurement of Lesions

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

5.4.4.2 Method of Assessment

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

5.4.4.3 CT/MRI Scan

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

5.4.4.4 Chest X-Ray

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

5.4.4.5 Clinical Lesions

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

5.4.4.6 Ultrasound

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

5.4.4.7 Endoscopy, Laparoscopy

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

5.4.4.8 Tumor Markers

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

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

5.4.5.1 Target Lesions

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

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

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

5.4.5.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.5.3 Non-target Lesions

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

5.4.6 Tumor Response Evaluation

Evaluation of Target Lesions

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

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an

absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

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

5.4.6.1 Target Lesions that Become "Too Small to Measure"

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

5.4.6.2 Target Lesions that Split or Coalesce on Treatment

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

As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

5.4.6.3 Evaluation of Non-target Lesions

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

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

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

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

5.4.6.4 Unequivocal Progression in Non-target Disease

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

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

5.4.7 New Lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example,

some 'new' bone lesions may be simply healing or flare of preexisting lesions. This is particularly important when the subject's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan reported as a 'new' cystic lesion, which it is not.

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

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

5.4.8 Response Criteria (RECIST 1.1)

For subjects who have measurable disease at baseline, Table 5.4.8-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.8-1: Time Point Response - Subjects With Target (± Non-target) Disease

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

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

5.4.8.1 Missing Assessments and Not Evaluable Designation

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

5.4.8.2 Confirmation of Scans

Verification of Response: Confirmation of response is not required since it will not add value to the interpretation of study results per RECIST 1.1.

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

5.4.9 Best Overall Response

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

For purposes of this study, the minimum scan time from baseline for determination of SD will be 9 weeks.

5.4.10 Duration of Objective Response

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

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn from study subjects assigned to all 3 treatment arms at the time points indicated in Table 5.5-1.

Table 5.5-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections (CA209067)

Study Day[a]	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
C1W1D1	0 (Predose)[b]	00:00	X	X	X	X
C1W1D1	1.0 (EOI-nivo)[c]	01:00	X			
C1W1D1	3.0 (EOI-ipi)[d]	03:00			X	
C1W3D1	0.0 (predose)[b]	00:00	X	X	X	X
C1W4D1	0.0 (predose)[b]	00:00	X	X	X	X
C2W1D1	0.0 (predose)[b]	00:00	X	X	X	X
C2W1D1	1.0 (EOI-nivo)[c]	01:00	X			
C2W1D1	3.0 (EOI-ipi)[d]	03:00			X	
C3W1D1	0.0 (predose)	00:00	X	X		
C4W1D1	0.0 (predose)[b]	00:00	X	X	X	X
C4W1D1	1.0 (EOI-nivo)	01:00	X	X		
First 2 Follow-up visits (approximately up to 100 days from the discontinuation of study drug	N/A	N/A	X	X		

[a] If a subject discontinues study dug treatment during the sampling period, they will move to sampling at the follow up visits. In the event of a missed dose, a single PK sample will be collected (to measure predose or trough serum concentration) within +/- 3 day period of the scheduled dosing day

[b] Predose: All pre-dose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab infusion.

[c] EOI-nivo: End of nivolumab Infusion. This sample should be taken immediately prior to stopping the nivolumab infusion (preferably within 2 minutes prior to end of infusion). If the end of nivolumab infusion is delayed, the collection of the infusion should be delayed accordingly.

[d] EOI-ipi: End of ipilimumab infusion. This sample should be taken immediately prior to stopping the ipilimumab infusion (preferably within 2 minutes prior to end of infusion.) 3 hour timepoint takes into account 30 min flush in between nivo and ipi dosing. If the end of ipilimumab infusion is delayed, the collection of this sample should be delayed accordingly.

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

5.6 Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab and/or nivolumab in combination with ipilimumab will be investigated in peripheral blood and in tumor specimens taken from all subjects prior to treatment and as outlined in Section 5.1. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. In addition, analyses of markers between the three treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs. prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with melanoma or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

5.6.1 Tumor Tissue Specimens

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

These tumor samples, as well as any solitary lesions that may have been surgically resected from subjects following an initial response (as described in section 3.4.3), may also be assessed for the expression of other immune or melanoma related genes, RNAs and/or proteins, as well as, the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to immunohistochemistry (IHC), qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, ipilimumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of

TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Tissue from the resected solitary lesions may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets therof.

5.6.2 Exploratory Serum Biomarkers

Blood samples for exploratory serum biomarker analyses will be drawn at the time points indicated in Section 5.1. Blood samples will be processed to collect serum and then put in frozen storage. Samples may be assessed by ELISA, seromics and/or other relevant multiplex-based protein assay methods for immune or melanoma-related factors that will predict for nivolumab or ipilimumab benefit or correlate with nivolumab or ipilimumab efficacy. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict or correlate with efficacy to nivolumab, ipilimumab or other immunotherapy, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors and microRNAs (such as, but not limited to, miR-513 and miR19b).

5.6.3 Peripheral Blood Mononuclear Cells (PBMCs)

Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Section 5.1 for additional details on the blood sample collection schedule) for PBMC preparation. Samples must be shipped within 48 hours to a BMS-designated central laboratory for processing.

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

5.6.4 Peripheral Blood RNA

While immunophenotyping of peripheral blood will provide valuable information on the modulation of the composition of immune cells in the periphery, gene expression analyses of RNA derived from whole blood may provide information on the broad effects of nivolumab and ipilimumab on immune modulation. Thus, genomic expression patterns of whole blood collected at baseline and during on-study treatment as specified in Table 5.1-2 may be assessed by Affymetrix microarray profiling, qRT-PCR or other gene expression profiling technology, with a particular emphasis on genes with relevant immune function. In addition, RNA or DNA derived from this peripheral blood sample may be assessed for rearrangements in the T cell receptor (TCR) in T cells within the peripheral blood. An assessment of somatic TCR rearrangements by PCR, sequencing or NextGen sequencing approach will provide information regarding the clonality of a T cell repertoire, which may change with nivolumab and/or ipilimumab treatment. In addition, baseline T cell repertoire may be predictive of nivolumab and/or ipilimumab benefit.

5.6.5 Whole Blood for SNP Assessment

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

5.7 Outcomes Research Assessments

HRQoL will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is the most commonly used QoL instrument in advanced melanoma clinical studies.

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

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

Work Productivity and Activity Impairment: General Health (WPAI:GH).

This questionnaire is a 6-item questionnaire yielding four different types of scores. The WPAI:GH was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work /reduced on-the-job effectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The recall period in all WPAI validation studies is 7 days. The general literature on recall burden suggests that a longer recall period would not be suitable for the type of information being elicited in the WPAI. In theory, a shorter recall period would improve accuracy of WPAI responses, but this has not been tested. Assessment of work productivity will be conducted at each site (or remotely) with the appropriately translated and validated version of the WPAI.

The quality of survival in patients after treatment discontinuation will be characterized by measuring the health related quality of life (HRQoL), using the EQ-5D with VAS as outlined in Table 5.1-4

All PRO instruments will be administered during on-study, and follow-up phases as outlined in Section 5.1, 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 Table 5.1-2, Table 5.1-3 and Table 5.1-4

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analyses of nivolumab and/or ipilimumab will be collected according to the schedule given in Table 5.5-1. Samples collected from subjects in each treatment arm will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab and/or ipilimumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab. (Neutralizing ADA testing conditioned upon assay availability.)

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

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

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

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

6.1 Serious Adverse Events

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

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

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

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

6.1.1 Serious Adverse Event Collection and Reporting

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

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

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

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

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

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

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

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

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

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

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

6.5 Overdose

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

Potential drug induced liver injury is defined as:

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee will be established to provide oversight and safety and efficacy considerations in protocol CA209067 and to 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. 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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size is calculated to compare OS between nivolumab and ipilimumab and to compare OS between the combination of nivolumab/ipilimumab and ipilimumab at a Type I error level of 0.025 (two-sided) for each comparison. Hochberg's procedure [57] will be applied to control the overall Type I error at an alpha of 0.05 (two-sided). The number of events and power are calculated assuming an exponential distribution in each treatment group.

Approximately 915 subjects will be randomized to the three treatment arms in a 1:1:1 ratio. For each OS comparison, at least 460 events in the two respective treatment arms provide at least 90% power to detect a hazard ratio (HR) of 0.72 with a type I error of 0.025 (two-sided). The HR of 0.72 corresponds to a 39% increase in the median OS, assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment arms. Assuming the distribution of events follows the alternative hypothesis, approximately 247 events in the control group and 213 in each of the experimental groups are expected.

In time-to-event trials, the final analysis typically occurs when a certain number of events, pooled across treatment arms, are observed such that the trial is adequate powered under the design assumptions. However, in the first-line ipilimumab melanoma trial, CA184-024, the projected trial duration of 34 months was very different from the actual trial duration of 54 months, with the event rate slowing dramatically in the last 18 months.[58] In order that such a phenomenon does not unduly delay the final analysis in the current trial, the analysis of both primary OS comparisons will be conducted when approximately 247 events (ie deaths) in the control group have been observed. This approach has the added effect of harmonizing the timing of the two comparisons. An external statistical group will be utilized to track the number of events in the control group and alert the sponsor when the required number of events has been observed for final analysis.

At the time of final analysis, the exact number of deaths in an experimental group will depend on the observed hazard ratio. Under a true hazard ratio of 0.72, observing meaningfully fewer than 213 deaths in an experimental group is a low probability outcome and would indicate a greater treatment effect relative to control, thus maintaining adequate power for that comparison.

Assuming a piecewise constant accrual rate (3 subjects during Month 1, 6 subjects during Month 2, 27 subjects/month during Months 3 to 4, 48 subjects/month during Months 5 to 6, 69 subjects/month after Month 6), it will take approximately 44.1 months to obtain the required number of deaths for the final OS analysis (17.0 months for accrual and 27.1 months for survival follow up). It is projected that an observed HR of 0.8114 or less corresponding to a 3.3 month or

greater improvement in median OS (14 vs. 17.3 months) for each comparison, would result in a statistically significant improvement in the final analysis of OS.

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 group.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- PK Subjects: All randomized subjects with available serum time-concentration data.
- Immunogenicity Subjects: All randomized subjects with available ADA data.
- Biomarker Subjects: All randomized subjects with available biomarker data.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

The primary objective will be measured by the endpoint of OS in all randomized subjects. OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. OS data will be collected continuously while subjects are on study medication and every 3 months via in-person or phone contact after discontinuation of study medication.

8.3.2 Secondary Endpoint(s)

The first secondary objective (to compare PFS between the experimental arms and the control group) will be measured by the endpoint of PFS. PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 Weeks until disease progression.

The second secondary objective (to compare ORR between the experimental arms and the control group) will be measured by the endpoint of ORR. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs

first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 Weeks until disease progression.

The third secondary objective (to evaluate differences in OS, PFS, and ORR between the two experimental arms) and will be measured by the endpoints of OS, PFS, and ORR.

The fourth secondary objective (to evaluate PD-L1 expression as a predictive biomarker) will be measured by the endpoint OS based on PD-L1 expression level. PD-L1 expression will be evaluated in tumor specimens collected prior to randomization.

The fifth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-C30 scales. HRQoL will be evaluated per Section 5.1

8.3.3 Exploratory Endpoint(s)

Duration of and time to response will be measured by the endpoints duration of objective response (DOOR) and time to objective response (TTOR). DOOR is defined as the time between the date of first response to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. TTOR is defined as the time from randomization to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Pharmacokinetics will be measured using serum concentration-time data.

Other exploratory endpoints for biomarkers, pharmacogenomics, and immunogenicity are described in Sections 5.6 and 5.8.

8.4 Analyses

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

Each of the two primary OS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in all randomized subjects using Hochberg's procedure[57] to address multiplicity. Hazard ratios (HR) and corresponding two-sided (1-adjusted α)% confidence intervals (CI) will be estimated using a Cox proportional hazards

model, with treatment group 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.

8.4.2.2 Secondary Endpoint Methods

If OS superiority is demonstrated for either comparison, a gatekeeping testing approach for the key secondary endpoints will be applied to additional experimental vs. control comparisons as described in the statistical analysis plan. The alpha level retained for testing of secondary endpoints will depend on whether one or both OS comparisons are positive and ensure that the overall type I error is adequately maintained.

PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided (1-adjusted α)% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage to compare each of the two experimental treatments to the control group. Associated odds ratios and (1-adjusted α)% CIs will be calculated. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental arms, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

The totality of OS results will be summarized in a single graphical display that includes Kaplan-Meier curves for the three treatment arms, the log-rank p-values for the two formal comparisons, the three HRs and corresponding CIs, and the three KM medians and corresponding CIs. PFS results will be summarized similarly.

PD-L1 IHC data and tumor sample characteristics will be listed and summarized. The distribution of PD-L1 expression will be investigated graphically by summary plots and individual subject plots. Summary statistics of PD-L1 expression by treatment group and across treatment groups will be provided. To assess the potential association between PD-L1 expression and OS, OS curves and medians with 95% CIs will be estimated using Kaplan-Meier methodology by treatment group for each PD-L1 expression quartile and for subjects with a missing or indeterminate PD-L1 IHC result. Potential associations with PFS and ORR will also be examined. If there is an indication of a meaningful association, additional analyses may be performed to further evaluate PD-L1 expression as a predictive biomarker.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, 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.

8.4.4 Pharmacokinetic Analyses

The concentration vs. time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug- drug interaction between nivolumab and ipilimumab will be studied by population PK approach. Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately.

8.4.5 Biomarker Analyses

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

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 group. Exploratory analyses may be performed to examine differences between the two groups.

8.4.7 Other Analyses

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

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

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

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

9.2.3 Case Report Forms

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

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

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

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

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

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb
BP	blood pressure

Term	Definition
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent clearance of free drug or clearance of free if (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)

Term	Definition
Ctrough	Trough observed plasma concentration
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
GC	gas chromatography
GCP	Good Clinical Practice
G criteria	adjusted R^2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h	hour

Term	Definition
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC	liquid chromatography
LDH	lactate dehydrogenase
ln	natural logarithm
Lz_Start	The time point starting the log-linear elimination phase defining ther terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life

Term	Definition
mg	milligram
Mg^{++}	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
µg	microgram
N	number of subjects or observations
Na^{+}	sodium
N/A	not applicable
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
ORR	Objective Response Rate
OS	Overall Survival
Pb	percent of bound drug
PD	pharmacodynamics
PFS	Progression Free Survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)

Term	Definition
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state

Term	Definition
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

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[58] Robert C, Thomas L, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med*. 2011 Jun 30;364(26):2517-26

APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

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.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

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. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the

subject's legally acceptable representative 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.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	**ZUBROD-ECOG-WHO**	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

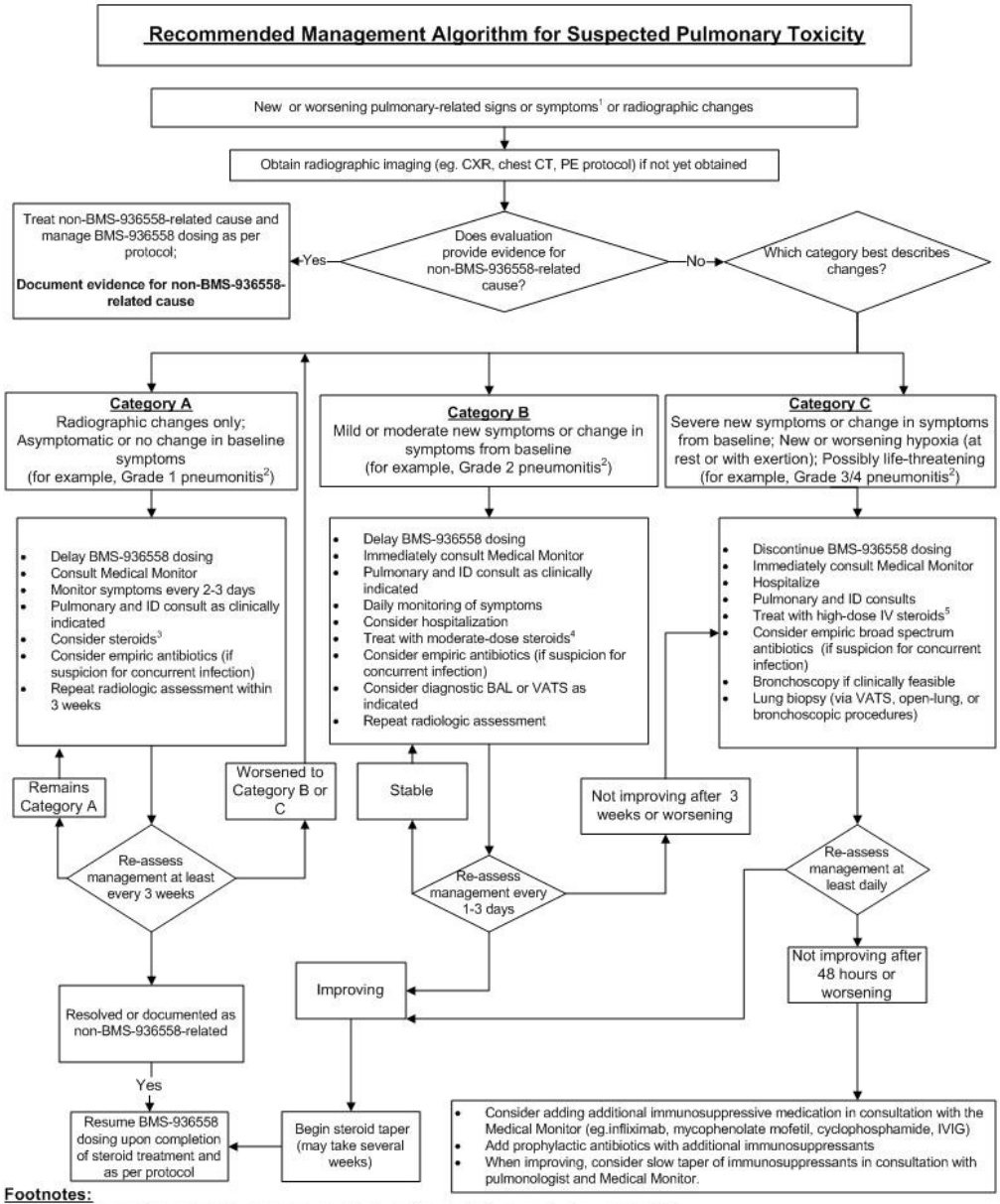
APPENDIX 3 M STAGE CATEGORIES FOR CUTANEOUS MELANOMA

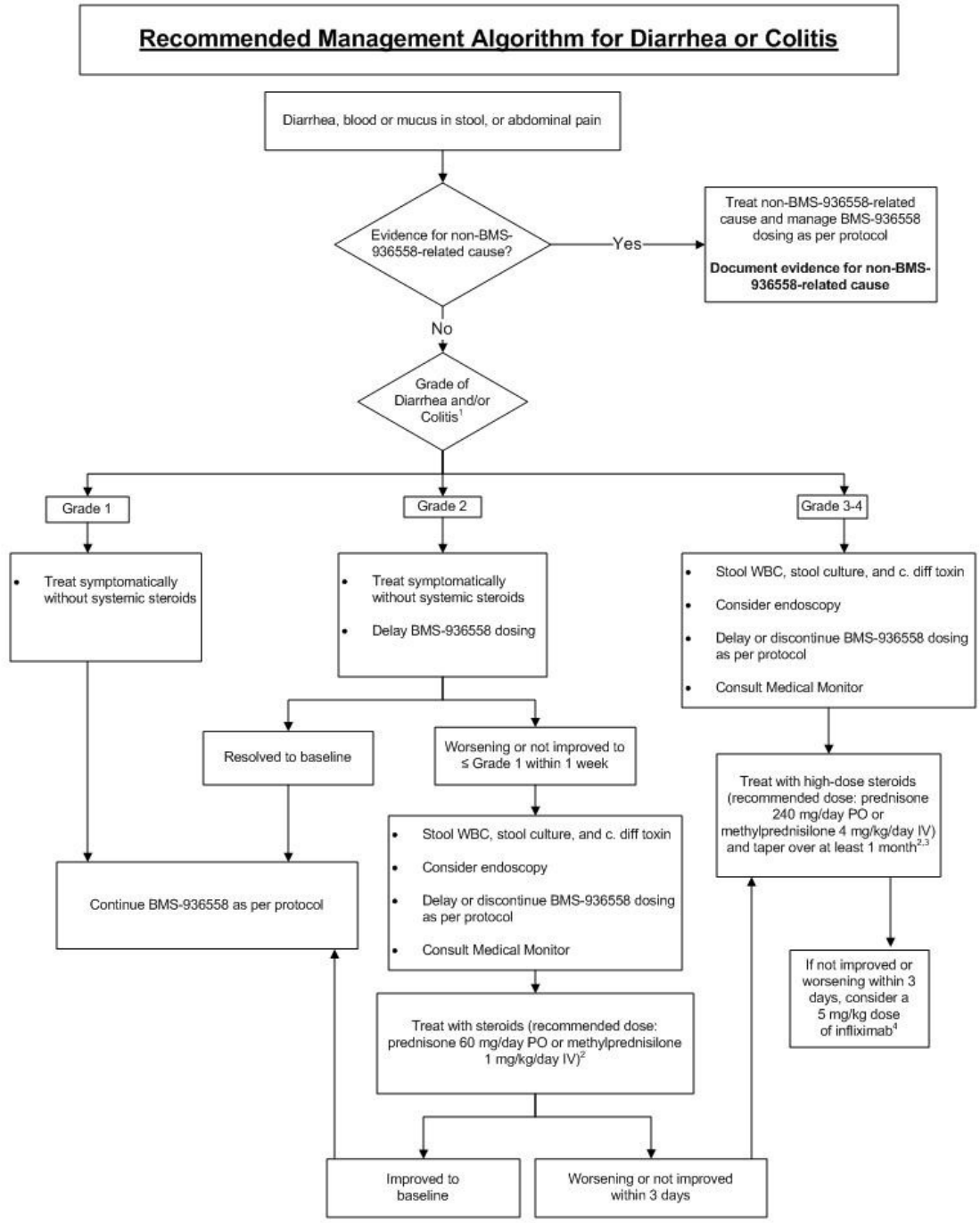
M Stage Categories for Cutaneous Melanoma[a]		
M	**Site**	**Serum LDH[b]**
M0	No distant metastasess	Not applicable
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

[a] Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009; 27:6199-6206.

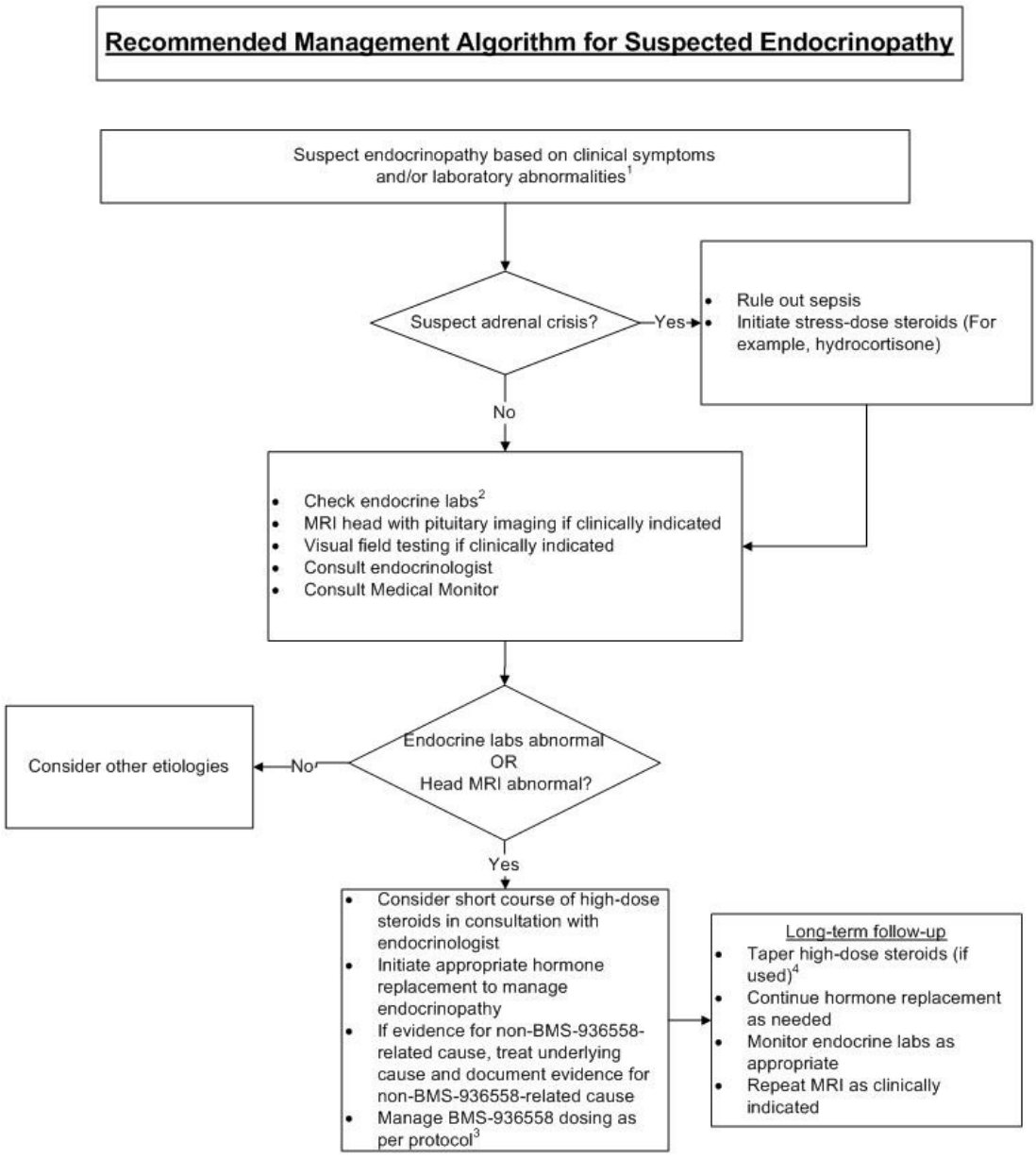
[b] LDH - Lactate dehygrogenase

APPENDIX 4 RECOMMENDED MANAGEMENT ALGORITHMS FOR SUSPECTED PULMONARY TOXICITY, DIARRHEA/COLITIS, SUSPECTED HEPATOTOXICITY, SUSPECTED ENDOCRINOPATHY, NEPHROTOXICITY, SKIN TOXICITY, AND NEUROLOGIC TOXICITY



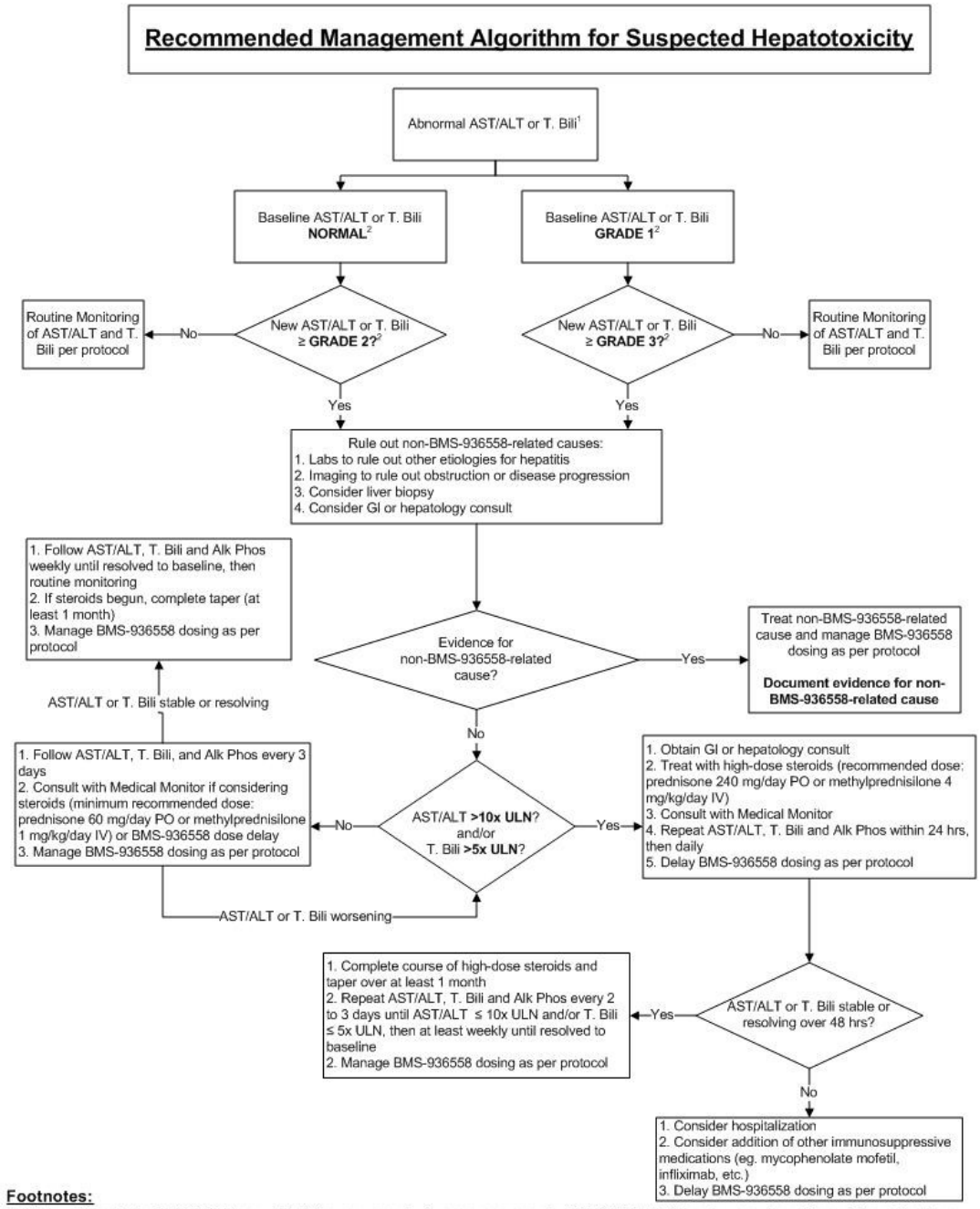


Footnotes:
1. Grading as per NCI CTCAE version 4.0. If both diarrhea and colitis are present, manage as per toxicity with higher grade.
2. If infection work-up is positive, do not give steroids, stop following algorithm and treat specific infection.
3. If re-treatment with BMS-936558 is allowed as per protocol after completion of steroid taper, consult with Medical Monitor if considering re-treatment.
4. Do not use infliximab if perforation or sepsis is present.



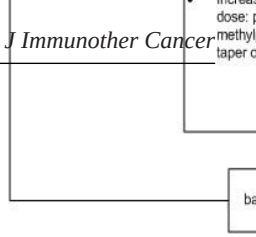
Footnotes:

1. Cases have typically been identified through routine monitoring of laboratories or as part of a work-up for symptoms such as fatigue.
2. It is important to draw labs at appropriate times; for example, certain labs should be drawn before giving steroids or at specific times of the day.
3. Upon resolution or adequate treatment of endocrinopathy, patients may continue BMS-936558 dosing with appropriate hormone replacement unless limited by protocol.
4. Patients may require chronic steroid replacement to maintain physiologic levels.

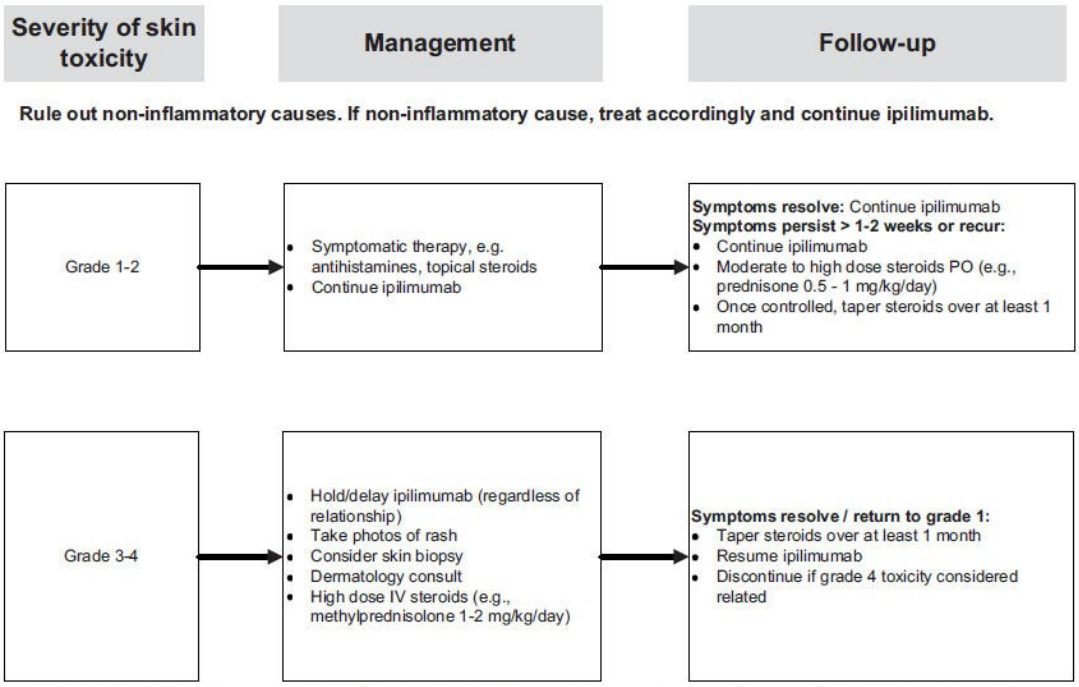


Footnotes:

1. If elevations in both AST/ALT and T. Bili are present, the management of BMS-936558 dosing may be different than if only an isolated AST/ALT or T. Bili abnormality is present and may not be dependent on baseline values. Refer to the specific protocol if concurrent elevations occur.
2. Grading as per NCI CTCAE version 4.0


dose: p
methyl
taper c
ba

Skin Toxicity Management Algorithm



Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

Neurological Toxicity Management Algorithm

Severity of neurological toxicity	Management	Follow-up
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue ipilimumab. Discontinue ipilimumab for any grade 3-4 motor neuropathy, regardless of relationship.		
Grade 1	• Continue ipilimumab	Continue monitoring the patient. If symptoms worsen, treat as below.
Grade 2	• Hold/delay ipilimumab • Treat symptoms per local guidelines	Resume ipilimumab when resolved / grade 1 If symptoms worsen, treat as below.
Grade 3-4 sensory	• Discontinue ipilmumab if considered related • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month
Grade 3-4 motor	• Discontinue ipilimumab **regardless of relationship** • Obtain neuro consult • Treat symptoms per local guidelines • High dose IV steroids (e.g., 1-2 mg/kg/ day methylprednisolone)	**Symptoms resolve / return to grade 2:** • Taper steroids over at least 1 month **Symptoms do not resolve or progress; atypical presention:** • Consider IVIg or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to oral corticosteroid (e.g., prednisone) at an equivalent dose at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of PO corticosteroids.

APPENDIX 5 GUIDANCE ON CONTRACEPTION

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

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

OPTION 1: Any TWO of the following methods

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

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

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

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

[b] Excludes progestin-only pills

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

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

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

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

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

UNACCEPTABLE METHODS OF CONTRACEPTION

Abstinence (including periodic abstinence)

No method

Withdrawal

Rhythm

Vaginal Sponge

Any barrier method without spermicide

Spermicide

Progestin only pills

Concomitant use of female and male condom

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

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

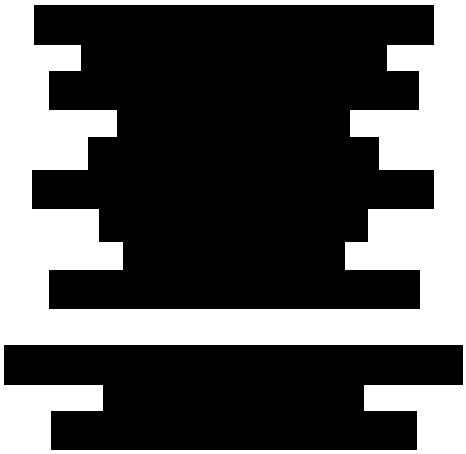
Protocol Number: CA209067
IND Number: 104,225
Ex-US Non-IND
EUDRACT Number 2012-005371-13
Date: 19-Mar-2013
Revised Date: 27-Oct-2017

Clinical Protocol CA209067

A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma.

(CheckMate 067: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 067)

Revised Protocol Number: 06
Incorporates Amendment: 11 and Administrative Letters 02, 03, 04, and 05



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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	20-Oct-2017	Incorporates Amendment 11 and Administrative Letters 02, 03, 04 and 05.
Amendment 11	20-Oct-2017	Prior to implementation of this amendment, following completion of the primary efficacy analysis, maintenance of the blind was no longer required for study purposes and all subjects were unblinded. The purpose of this amendment is to provide instructions for unblinded subjects remaining on study treatment or in follow-up.
Administrative Letter 05	26-Jul-2017	Change in Medical Monitor
Administrative Letter 04	17-Jul-2017	Change in Medical Monitor
Administrative Letter 03	10-Jul-2017	Change in Medical Monitor
Administrative Letter 02	02-Feb-2017	Update to Medical Monitor Address
Revised Protocol 05	12-Oct-2016	Incorporates Amendment 10
Amendment 10	12-Oct-2016	The main purpose of this protocol amendment is necessary following a recent update to the Nivolumab Investigator's Brochure version 15, Erratum 01, including those related to the use of contraceptives, and updated Appendix 5. Additionally, updated Tumor Assessment scan frequency in the Follow-up and Survival phase.
Revised Protocol 04	19-May-2015	Incorporates Administrative letter 01 and Amendment 08
Amendment 08	19-May-2015	The purpose of this amendment is to allow for future collection of survival status outside of the protocol-defined windows if necessary, correct errors and update Appendix 5 Methods of Contraception as well as SAE reporting language.
Administrative letter 01	24-Feb-2015	Change in Study Director/Medical Monitor
Revised Protocol 03	16-Jan-2015	Incorporates Amendment 07
Amendment 07	16-Jan-2015	The main purpose of Amendment 07 is to add the collection of radiographic images for review by an independent radiological review committee. No other changes are included in this amendment.
Revised Protocol 02	27-Jun-2014	Incorporates Amendment 06
Amendment 06	27-Jun-2014	The main purpose of Amendment 06 is to change the secondary objective to add PFS as a co-primary objective. • Additional modification are as described below: • Revise Research Hypothesis, Study Rationale, Primary Endpoints to include PFS as a co-primary objective/endpoint. • Add rationale for inclusion of PFS as a co-primary endpoint. • Revise statistical section 8 to include analyses related to PFS.

Document	Date of Issue	Summary of Change
Revised Protocol 01	20-Aug-2013	Incorporates Amendment 04
Amendment 04	20-Aug-2013	The main purpose of the first global amendment is to add a recommendation to perform an optional tumor biopsy when assessing whether to treat beyond progression per a Health Authority request. This biopsy can be used to assess the impact of treatment on relevant melanoma biomarkers including BRAF mutation status and investigate potential mechanisms of resistance to immunotherapeutic agents. Additional modifications are as described below: • Allow palliative radiotherapy and palliative surgery if the following criteria are met: ◦ The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression. ◦ The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record. • Asymptomatic elevations in amylase and lipase not associated with symptoms or clinical manifestations of pancreatitis were removed from the dose delay or discontinuation criteria. It is considered acceptable for the following reasons: ◦ Asymptomatic elevations of amylase or lipase have not been proven to have independent clinical consequence or predict for development or severity of pancreatitis ◦ A wide variation of asymptomatic elevations in amylase or lipase can occur on a day-to-day basis, limiting the utility of interpreting the amylase or lipase elevations in isolation. • Updated the Adverse Event Management Algorithms to be consistent with the Nivolumab IB v.12 • Add background information on opportunistic infections and recommendations for prophylactic antibiotics in the setting of greater than 4 weeks of corticosteroid or immunosuppressant administration • Clarify that either HCV antibody or HCV RNA testing is allowed to determine HCV status • Clarify exclusion criteria to exclude only subjects that participated in a blinded Phase 3 ipilimumab study • Incorporate other minor changes to correct and/or clarify protocol requirements
Amendment 01	19-Mar-2013	PGx
Original Protocol	19-Mar-2013	Not applicable

SYNOPSIS

Clinical Protocol CA209067

Protocol Title: A Phase 3, Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab Versus Ipilimumab Monotherapy in Subjects with Previously Untreated Unresectable or Metastatic Melanoma. (CheckMate 067: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 067)

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

- Nivolumab (BMS-936558) monotherapy administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or
- Nivolumab administered IV over 60 minutes at 1 mg/kg combined with ipilimumab administered IV over 90 minutes at 3 mg/kg every 3 weeks for 4 doses followed by nivolumab administered IV over 60 minutes at 3 mg/kg every 2 weeks until progression or
- Ipilimumab monotherapy administered IV over 90 minutes at 3 mg/kg every 3 weeks for a total of 4 doses

Study Phase: 3

Research Hypothesis: Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve progression free survival and overall survival compared to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma.

Objectives:

Primary Objective:

- To compare the progression free survival (PFS) and overall survival (OS) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma

Secondary Objectives:

- To compare Objective Response Rate (ORR) of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with advanced melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for PFS and OS.
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

Exploratory Objectives:

Exploratory objectives are listed in Section 1.3.3 of the protocol.

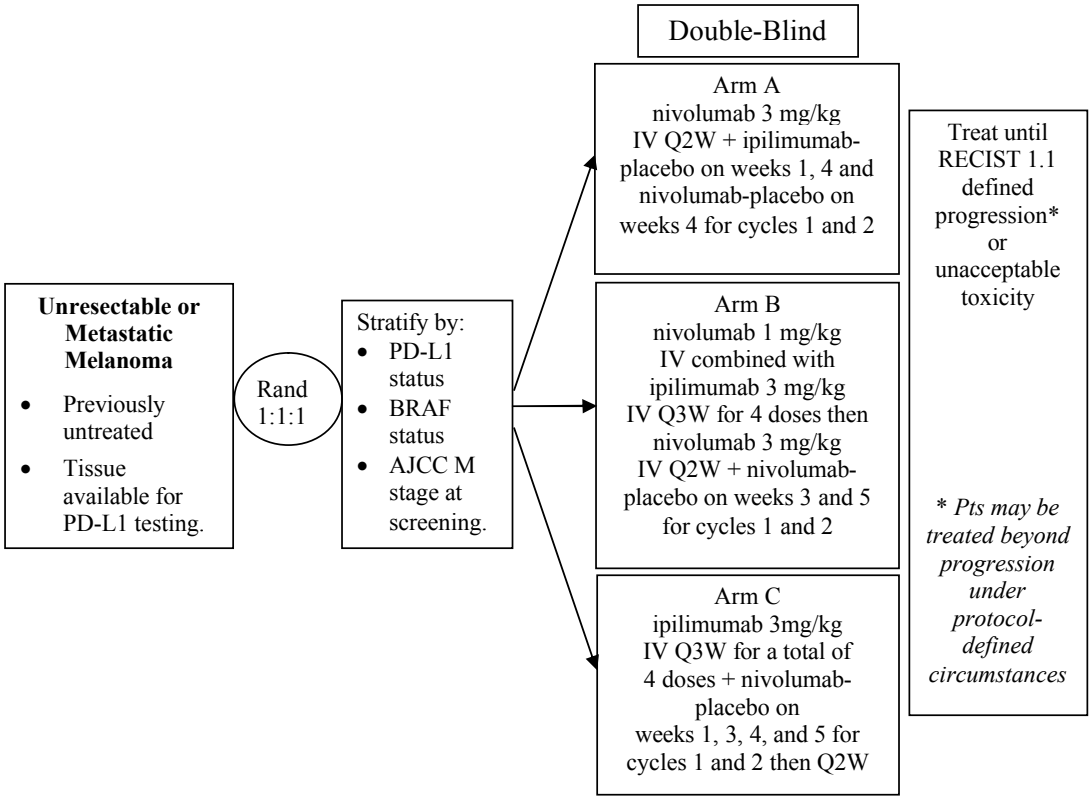
Study Design:

This is a Phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated unresectable or metastatic melanoma. Subjects must have stage III (unresectable) or stage IV melanoma, as per the American Joint Committee on Cancer (AJCC) staging system, and must not have received prior therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization. Subjects will be randomized 1:1:1 and stratified by PD-L1 status (positive

vs. negative/indeterminate), BRAF Status (BRAF mutation positive, BRAF wildtype), and AJCC M stage (M0/M1a/M1b vs. M1c). One cycle of treatment is defined as six weeks. Subjects will be treated with one of the following:

- Arm A: nivolumab 3 mg/kg IV Q2W + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2
- Arm C: ipilimumab 3mg/kg IV Q3W for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4, and 5 for cycles 1 and 2 then Q2W. Note that, in the unblinded portion of the study, per Amendment 11, subjects in Arm C will no longer receive nivolumab-placebo infusions, but will enter the follow-up phase.

One cycle of treatment will be defined as six weeks. Dose reductions will be not be allowed.



Prior to implementation of Amendment 11, following completion of the primary efficacy analysis, maintenance of the blind was no longer required for study purposes and all subjects were unblinded. The purpose of Amendment 11 is to provide instructions for unblinded subjects remaining on study treatment or in follow-up.

Study Population:

Key Inclusion Criteria:

- ECOG PS 0 or 1.
- Histologically confirmed stage III (unresectable) or stage IV melanoma, as per AJCC staging system.
- Treatment naïve patients (ie, no prior systemic anticancer therapy for unresectable or metastatic melanoma). Note that prior adjuvant or neoadjuvant melanoma therapy is permitted. Note that prior adjuvant or neoadjuvant melanoma therapy is permitted if it was completed at least 6 weeks prior to randomization, and all related adverse events have either returned to baseline or stabilized.
- Measurable disease by CT or MRI per RECIST 1.1 criteria.
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.
- Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period

Key Exclusion Criteria:

- Active brain metastases or leptomeningeal metastases. Subjects with brain metastases are eligible if these have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 8 weeks after treatment is complete and within 28 days prior to first dose of study drug administration. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.
- Ocular melanoma.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids, and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

Study Assessments:

Progression free survival and overall survival are co-primary endpoints of the study. Subjects will be assessed for response by CT or MRI beginning at 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for up to Week 49 and then every 12 weeks (± 1 week) until progression or treatment discontinuation, whichever occurs later. Progression free survival is defined as the time between the date of randomization and the first date of documented progression or death, whichever occurs first. Overall survival is defined as the time from randomization to the date of death.

Statistical Considerations:

Sample Size:
Approximately 915 subjects will be randomized to three treatment arms in a 1:1:1 ratio. The sample size of the study accounts for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS), with an alpha allocation of 0.01 for PFS and 0.04 for OS. The number of events and power are calculated using statistical models based on PFS and OS data external to this study.

Formal analyses of PFS and OS will be conducted at different timepoints.

- The PFS analysis is targeted to occur after all subjects have 9 months follow-up per sample size and power considerations (Section 8.1.1). However, the required minimum follow-up for analysis of PFS is 6 months.
- The OS analysis is targeted to occur after all subjects have 28 months follow-up per sample size and power considerations (Section 8.1.2). However, the required minimum follow-up for analysis of OS is 22 months.

For each PFS comparison, the number of events projected to be observed at 9 months follow-up provide approximately 83% power to detect an average hazard ratio (HR) of 0.71 with a Type I error of 0.005 (two-sided). This modeling assumes PFS medians of 2.8 and 3.1 months, 6 month PFS rates of 21.6% and 36.9%, and 12 month PFS rates of 12.8% and 26.9% in the control arm and experimental arms, respectively. Assuming the distribution of events follows the alternative hypothesis, approximately 266 PFS events in the control group and 223 PFS events in each of the experimental groups are expected at the time of analysis.

For each OS comparison, the number of events projected to be observed at 28 months of follow-up provide approximately 99% power to detect an average HR of 0.65 with a Type I error of 0.02 (two-sided). This modeling assumes OS medians of 10.2 and 17.2 months, 12 month OS rates of 43.9% and 62.1%, and 24 month OS rates of 24.4% and 39.6% in the control arm and experimental arms, respectively. Assuming the distribution of events follows the alternative hypothesis, approximately 240 OS events in the control group and 202 OS events in each of the experimental groups are expected at the time of analysis.

Endpoints:

Primary Endpoint:

PFS and OS are co-primary endpoints for this study. Formal analyses of PFS and OS will be conducted at different time points with PFS being analyzed first followed by analyses of OS.

Secondary Endpoints:

ORR is a key secondary endpoint. If PFS superiority is demonstrated for either experimental versus control comparison, a gatekeeping testing approach for ORR will be applied as described in the statistical analysis plan.

Analyses:

At the PFS analysis timepoint, each of the two primary PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided 99.5% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

At the OS analyses timepoint, each of the two primary OS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage in all randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided 98% CIs will be estimated using a Cox proportional hazards model, with treatment group 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.

The secondary endpoint of ORR will only be tested at the PFS analysis timepoint as part of a testing hierarchy. These ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage to compare each of the two experimental treatments to the control group. Associated odds ratios and (1-adjusted α)% CI will also be calculated. Additionally, ORRs and their corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment groups.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental groups, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

The totality of PFS and OS results will be summarized in a single graphical display that includes Kaplan-Meier curves for the three treatment groups, the log-rank p-values for the two formal comparisons, the three HRs and corresponding CIs, and the three KM medians and corresponding CIs.

Descriptive analyses will be performed to evaluate the potential of PD-L1 expression as a predictive biomarker for PFS and OS.

EORTC QLQ C-30 global health status/QoL composite scale data and the remaining EORTC QLQ C-30 scale data will be summarized by time point using descriptive statistics for each treatment group.

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1 INTRODUCTION AND STUDY RATIONALE

This is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. This study will allow for direct comparison of the clinical benefit, as measured by progression free survival (PFS) and overall survival (OS), provided by nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy. If the safety profile is acceptable and nivolumab monotherapy or nivolumab combined with ipilimumab is shown to improve OS, this study would support the approval of nivolumab or nivolumab combined with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma.

1.1 Study Rationale

CA209067 (CheckMate 067, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. Ipilimumab was chosen as the comparator because it is FDA and EMA approved in subjects with unresectable or metastatic melanoma and currently utilized for previously untreated melanoma patients in the US. It is the only FDA or EMA approved therapy for unresectable or metastatic melanoma that has demonstrated overall survival benefit in a randomized Phase 3 trial and is not BRAF status restricted. Nivolumab monotherapy was chosen as one of the experimental arms because of a favorable risk-benefit ratio assessed in the large Phase 1 study (MDX1106-03/CA209003). The combination of nivolumab and ipilimumab was chosen as an experimental arm because of the preliminary evidence from the Phase 1 study CA209004 suggesting synergy between nivolumab and ipilimumab resulting in a higher frequency of patients with increased tumor burden reduction. Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on their individual risk-benefit ratio.

1.2 Research Hypothesis

Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve progression free survival and overall survival when compared to ipilimumab monotherapy in previously untreated subjects with unresectable or metastatic melanoma

1.3 Objectives(s)

1.3.1 Primary Objectives

- To compare PFS and OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.

1.3.2 Secondary Objectives

- To compare ORR of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for OS
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

1.3.3 Exploratory Objectives

- To evaluate duration of and time to objective response of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab in subjects with unresectable or metastatic melanoma
- To assess the overall safety and tolerability of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab monotherapy in subjects with unresectable or advanced melanoma
- To characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination with nivolumab
- To characterize the immunogenicity of nivolumab and nivolumab combined with ipilimumab
- To evaluate pharmacokinetic drug-drug interaction between nivolumab and ipilimumab
- To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) of nivolumab and/or nivolumab combined with ipilimumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes.
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events
- To assess changes in health status and work and activity impairment in treatment groups using the EuroQoL EQ-5D and the Work Productivity and Activity Impairment questionnaire (WPAI-GH) respectively
- To describe the quality of survival in patients after treatment discontinuation using the EuroQoL EQ-5D .

1.4 Product Development Background

1.4.1 Nivolumab Mechanism of Action

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune

response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. This functions by aborting the emergence of tumors as they arise and/or causing tumor shrinkage where it is present. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immune surveillance and an effective immune response.[1] This evasion may occur by exploiting any of the checkpoints that control the regulatory immune response, including display of antigens and control of co-stimulatory pathways that affect the proliferation of cells involved in immunity. Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system - either directly by stimulation of immune cells by antibodies directed to receptors on T and B cells or indirectly by cytokine manipulation. T-cell stimulation is a complex process involving the integration of numerous positive, as well as negative, costimulatory signals in addition to antigen recognition by the T-cell receptor (TCR).[2] Collectively, these signals govern the balance between T-cell activation and tolerance to antigens.[1]

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell costimulary receptors that also includes CD28, CTLA-4, ICOS, and BTLA.[2] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[3,4] PD-1 delivers a negative signal by the recruitment of a protein tyrosine phosphatase SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[5,6] PD-1 is primarily expressed on activated T cells, B cells and myeloid cells.[7]

Further evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy, a lupus-like syndrome with arthritis and nephritis, and accelerated diabetes mellitus.[8,9,10] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain and many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[11,12] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Preclinical animal models of tumors have shown that blockade by PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. Antitumor activity by PD-1 blockade functions in PD-L1+ tumors as well as in tumors that are

negative for the expression of PD-L1.[13,14,15,16,17,18] This suggests that host mechanisms (ie, expression of PD-L1 in antigen-presenting cells) limit the antitumor response. Consequently, both PD-L1 positive and negative tumors may be targeted using this approach. In humans, constitutive PD-L1 expression is normally limited to macrophage-lineage cells, although expression of PD-L1 can be induced on other hematologic cells as well, including activated T cells. However, aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies.[19,20,21,22,23,24,25] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[7] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[26] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by IHC) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness.[20,24] Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression. In addition, in multivariate analysis, high expression of PD-L1 is correlated to have a worse overall survival rate compared to low expression levels of PD-L1.[27]

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.[28] The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA.

These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by nivolumab is therefore considered a promising immunotherapeutic option.

1.4.2 Melanoma: Background

Melanoma is the most serious form of skin cancer and strikes adults of all ages. The 5-year prevalence of melanoma in the European Union (EU) is ~159,000 patients with an incidence of ~ 41,000 per year and ~ 11,000 deaths annually as described in the World Health Organization (WHO) Europe region.[29] Melanoma accounts for ~ 5% of all new cases of cancer in the United States (US). The incidence of melanoma continues to rise by almost 3% per year in the US. This translates to 76,000 new cases a year with 9,000 associated deaths. The male-to-female incidence ratio of melanoma is 1.4:1, respectively.[30] The five-year survival rate is 15% for late-stage disease.[31] The lifetime risk of developing invasive melanoma has been dramatically increasing and the overall mortality from melanoma continues to rise.[32,33,34]

Yervoy™ (ipilimumab), an anti-cytotoxic T lymphocyte associated antigen-4 (CTLA-4) blocking antibody, and vemurafenib, a BRAF inhibitor, are the only agents approved for

unresectable or metastatic melanoma that have demonstrated overall survival (OS) benefit in randomized, comparative Phase 3 registrational trials.

In the Phase 3 study MDX010-20, 3 mg/kg ipilimumab monotherapy demonstrated a hazard ratio (HR) of 0.66 and a 4-month median OS benefit compared to gp100 vaccine in pretreated advanced melanoma subjects.[35] Grade 3 to 4 immune-related adverse events (AEs) included colitis (5.3%), diarrhea (4.6%), endocrinopathies (3.8%), and rash (0.8%). In the US, 3 mg/kg of ipilimumab was approved for unresectable or metastatic melanoma based on data from MDX010-20 without restriction to line of therapy, supported by the results of an additional Phase 3 randomized ipilimumab clinical study, CA184-024. In the CA184024 trial, treatment-naïve advanced melanoma subjects treated with 10 mg/kg ipilimumab in combination with dacarbazine (DTIC) demonstrated an HR of 0.72 and a 2-month median OS benefit compared with dacarbazine monotherapy.[36] In the EU, 3 mg/kg of ipilimumab is currently approved for the treatment of advanced (unresectable and metastatic) melanoma in adults who have received prior therapy.

Approximately 50% of cutaneous melanoma cases are BRAF V600 mutation positive. Vemurafenib is approved in the US and in the EU for the treatment of BRAF V600 mutation-positive advanced melanoma subjects regardless of line of therapy.[37,38] In the BRIM-3 Phase 3 study, vemurafenib demonstrated a 48% response rate and an increased OS benefit compared to dacarbazine with a HR of 0.37, but with inadequate follow-up beyond 7 months to provide a reliable Kaplan-Meier OS estimate in treatment-naïve advanced melanoma patients.[39] Common and significant Grade 2 to 3 AEs associated with vemurafenib include arthralgia (21%), rash (18%), fatigue (13%), photosensitivity (12%), squamous-cell carcinoma (12%), keratoacanthomas (8%), and nausea (8%).

Besides these two agents, no other agent has demonstrated an overall survival benefit in a Phase 3 randomized study. In the EU, dacarbazine is indicated as systemic therapy for the treatment of advanced melanoma regardless of line of therapy. Dacarbazine demonstrates an objective response rate (ORR) of 13% with a median OS ranging from 5.6 to 11 months among 8 randomized studies; and a 1-year OS ranging from 20% to 30% among 5 randomized studies.[40] The primary toxicities associated with dacarbazine are hematological including Grade 3 to 4 neutropenia (16%), lymphopenia (9%), leukopenia (8%), and thrombocytopenia (6%). Additionally, the most common non-hematological toxicities associated with dacarbazine include Grade 3 to 4 fatigue (5%), nausea (3%), and vomiting (2%).[41] Additional palliative therapies for unresectable or metastatic disease include cytostatics such as taxanes, fotemustine or others, cytokines (Interferons, Interleukin-2 [IL-2]), or combinations.[42]

1.4.3 Summary of Results from the Ipilimumab and Nivolumab programs

1.4.3.1 Preclinical Summary of Nivolumab combined with Ipilimumab

Preclinical data indicate that the combination of PD-1 and CTLA-4 receptor blockade may improve antitumor activity. In vitro combinations of nivolumab plus ipilimumab increase IFN-γ

production 2- to 7-fold over either agent alone in a mixed lymphocyte reaction. Increased antitumor activity of the combination was also observed in 3 of 5 syngeneic murine cancer models. In a murine melanoma vaccine model, blockade with either CTLA-4 or PD-1 antibodies increased the proportion of CTLA-4 and PD-1-expressing CD4/CD8 tumor infiltrating T effector cells, and dual blockade increased tumor infiltration of T effector cells and decreased intratumoral T regulatory cells, as compared to either agent alone[43].

Preclinically, a 4-week toxicity study of nivolumab in combination with ipilimumab conducted in cynomolgus monkeys demonstrated that the combination of nivolumab and ipilimumab resulted in dose-dependent gastrointestinal (GI) toxicity. Histologic findings included inflammatory changes in the large intestine, which increased in incidence and severity in a dose-dependent manner. GI toxicity/colitis was not observed in cynomolgus monkeys administered nivolumab alone, but was observed in monkeys receiving ipilimumab. Nivolumab in combination with ipilimumab was also associated with lymphoid hypocellularity of the cortex and/or medulla of the thymus and with acinar cell degranulation in the pancreas. Additional findings included interstitial mononuclear cell infiltrates in the kidneys, portal mononuclear cell infiltrates in the liver and myeloid hypercellularity in the bone marrow. Nivolumab in combination with ipilimumab at the high-dose level (ie, 50 mg/kg and 10 mg/kg, respectively) was associated with the death of 1 animal, attributed to acute gastric dilatation without histopathological evidence of colitis upon pathology evaluation of the GI tract.

1.4.3.2 Summary of Safety

Ipilimumab Monotherapy

In MDX010-20, the ipilimumab monotherapy arm was administered 3 mg/kg ipilimumab every 3 weeks for four doses. In this arm, there were 79% drug related adverse events, with 21% being Grade 3/4 and 3/131 (2%) Grade 5. The most frequent adverse events of interest were rash (30%), pruritis (33%), diarrhea (33%), colitis (8%), endocrine disorders (9%), AST/ALT increased (2%), and hepatitis (1%). Any grade immune related adverse events were 60% and the Grade 3/4 immune related adverse events for the same cohort was 13% with the most frequent adverse events being diarrhea (5%), colitis (5%), rash (2%), and endocrine disorders (3%).

Additional details on the safety profile of ipilimumab, including results from other clinical studies, are also available in the ipilimumab IB.

Nivolumab Monotherapy

One study has contributed most to the clinical experience with nivolumab monotherapy in subjects with melanoma and other solid malignancies. CA209003 is an ongoing Phase 1 open label, multiple dose escalation study in 304 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3 or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. As of 03-Jul-2012, a total of 107 melanoma subjects were treated with nivolumab in the dose range of 0.1-10 mg/kg.

No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 72.4% of subjects. The most frequent nivolumab related AEs occurring in ≥ 5% of subjects included: fatigue (25.7%), rash (13.5%), diarrhea (11.8%), pruritis (10.2%), nausea (7.9%), decreased appetite (7.9%), hemoglobin decreased (5.9%) and pyrexia (5.3%). The majority of events were low grade, with grade 3-4 drug related AEs observed in 14.8% of subjects. The most common Grade 3-4 drug-related AEs occurring in ≥ 1% of subjects were: fatigue (1.6%), lymphopenia (1.3%), abdominal pain (1%), diarrhea (1%), hypophosphatemia (1%) and pneumonitis (1%). At least one SAE was reported for 150 (49.3%) of the 304 subjects at all dose levels. Grade 3-4 SAEs were reported for 23 subjects (7.6%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Additional select treatment-related AEs have occurred with low frequency (< 5%) but are considered clinically meaningful, as they require greater vigilance for early recognition and prompt intervention. These AEs include: ALT increased (4.3%), AST increased (3.6%), pneumonitis (3.3%), hypothyroidism (3.0%), hyperthyroidism (1.3%), renal failure (1.0%), adrenal insufficiency (0.7%) and colitis (0.7%). Grade 3-4 events of pneumonitis were reported in 3 subjects (1.0%) as described above (1 event was Grade 4). Grade 3 events of colitis, ALT increased, and AST increased were reported in 2 subjects (0.7%) each. Grade 3 events of adrenal insufficiency, hyperthyroidism, and hypothyroidism were reported in 1 subject (0.3%) each. Treatment-related AEs leading to discontinuation were reported in 18 (5.9%) of the 304 treated subjects on CA209003. The only events reported in more than 1 subject were pneumonitis (4 subjects; 1.3%) and hepatitis (2 subjects; 0.7%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis.

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported.[44] The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in nivolumab exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with nivolumab during pregnancy.

Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

Nivolumab Combined with Ipilimumab

In the Phase 1 study CA209004, ascending doses of nivolumab have been studied concomitantly with ascending doses of ipilimumab in subjects with unresectable or metastatic melanoma. In each arm in this multi-arm study, ipilimumab was administered once every 3 weeks for 4 doses with nivolumab administered once every 3 weeks for 8 doses. Starting at week 24, ipilimumab and nivolumab were administered once every 12 weeks for 8 doses. The three initial dose-escalation cohorts consisted of Cohort 1 (nivolumab 0.3 mg/kg plus ipilimumab 3 mg/kg; n=14), Cohort 2 (nivolumab 1.0 mg/kg plus ipilimumab 3 mg/kg; n=17) and

Cohort 3 (nivolumab 3.0 mg/kg plus ipilimumab 3 mg/kg; n=6). Later, the study was amended to include Cohort 2a which evaluated nivolumab 3 mg/kg plus ipilimumab 1 mg/kg (n-16).

The following DLTs were observed in Cohort 1 - Grade 3 elevated AST/ALT (1 subject); in Cohort 2 - Grade 3 uveitis (1 subject) and Grade 3 elevated AST/ALT (1 subject) and in Cohort 3 - Grade 4 elevated lipase (2 subjects) and Grade 3 elevated lipase (1 subject). Based on these data, Cohort 2 was identified as the maximum tolerated dose (MTD) and Cohort 3 exceeded the MTD.

As of 15-Feb-2013, a total of 53 melanoma subjects were treated with nivolumab combined with ipilimumab in CA209004 across cohorts 1, 2, 2a, and 3. At least one AE regardless of causality has been reported in 98% of subjects treated. The most common (reported at > 10% incidence) treatment related AEs (any Grade %; Grade 3-4 %: 93; 53) are rash (55; 4), pruritus (47; 0), vitiligo (11; 0), fatigue (38; 0), pyrexia (21, 0), diarrhea (34; 6), nausea (21, 0), vomiting (11, 2), ALT increased (21; 11), AST increased (21; 13), lipase increased (19; 13), amylase increased (15, 6), headache (11, 0), and cough (13, 0).

The majority of AEs leading to discontinuation (regardless of causality) were Grade 3 or 4 (reported in 11 of 53 subjects, 21%). Grade 3 events included lipase increased, ALT increased, AST increased, troponin I increased, colitis, diverticular perforation, pancreatitis, tachycardia, renal failure acute, choroiditis, autoimmune disorder, and pneumonitis. One subject each discontinued due to Grade 4 events of blood creatinine increased and AST increased. No drug-related deaths were reported.

Adverse Event Management Algorithms

Because of the potential for clinically meaningful nivolumab or ipilimumab related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, GI, hepatotoxicity, endocrinopathy, skin toxicity, neurological toxicity and renal toxicity. Prompt interventions are recommended according to the management algorithms and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

Given the blinded nature of the study and in order to standardize the management across all three arms, the recommendations are to follow the BMS-936558 (nivolumab) adverse event algorithms and not the ipilimumab IB algorithms.

The algorithms recommended for utilization in CA209067 are contained in Appendix 4.

As of 03-Apr-2013, three subjects out of approximately 1200 patients on nivolumab clinical trials have developed opportunistic infections (2 cases of Aspergillus pneumonia, and 1 case of Pneumocystis jiroveci pneumonia) after receiving prolonged treatment with high dose steroids for nivolumab-related adverse events. Details of these cases are available in the Investigator Brochure. Because of the potential for opportunistic infections with prolonged high dose corticosteroids administration, the following recommendations should be considered for subjects with inflammatory events expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage the adverse event:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients that develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab, including results from other clinical studies, are available in the IB.

1.4.3.3 Summary of Clinical Activity

Ipilimumab Monotherapy

In melanoma, a completed Phase 3 study (MDX010-20) has demonstrated a clinically meaningful and statistically significant survival benefit in pre-treated advanced melanoma. The study compared the overall survival (OS) of ipilimumab plus a melanoma-specific vaccine (gp100) to that of gp100 alone. A second comparison defined the OS of ipilimumab alone vs gp100 alone. Both comparisons demonstrated statistically significant improvements in OS ($p = 0.0004$ and 0.0026, respectively). The 1-year survival for the two ipilimumab-containing groups, respectively, was 44% and 46% respectively, compared to 25% for the gp100 control group. The 2-year survival was 22%, 24% and 14% respectively. The median survival was 10, 10.1, and 6.4 months, for ipilimumab plus gp100, ipilimumab monotherapy, and gp100 monotherapy, respectively.

Nivolumab Monotherapy

In CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 10 mg/kg).

In CA209003, as of the clinical cut-off date of 03-Jul-2012, a total of 304 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on modified RECIST 1.1, has been reported at all dose levels. No responses (CR or PR) have been reported in subjects with colorectal carcinoma or castrate-resistant prostate cancer.

Among 106 patients with advanced melanoma who received nivolumab and were evaluable for response, the preliminary objective response rates were 6/17 (35%), 5/18 (28%), 11/34 (32%), 7/17 (41%), and 4/20 (20%) for melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Duration of response range from 3.6 to 11.2, 1.8 to 9.2, 1.9 to 24.9, 9.2 to 22.4, and 17.0 to 25.7 months in the melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively. Stable disease ≥ 24 weeks occurred in an additional 1/18 (6%), 4/34 (12%), 1/17(6%) melanoma subjects at 0.3, 1, and 3 mg/kg, respectively. Finally, the PFS-24 week was

41%, 33%, 48%, 55%, and 30% in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.

Nivolumab Combined with Ipilimumab

As of the 15-Feb-2013 clinical cut-off in CA209004, of the 52 subjects evaluable for response, 21 subjects (40%) had an objective response by modified World Health Organization (mWHO) criteria. In an additional 2 subjects (4%) there was an unconfirmed objective response. In Cohort 1 (0.1 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 14 evaluable subjects had an objective response by mWHO (21%); 1 CR and 2 PRs with an additional PR by immune-related mWHO criteria (irPR).[55] In Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab), 9 out of 17 evaluable subjects had an objective response by mWHO (53%; 3 CRs (18%), 6 PRs (35%) with two additional subjects experiencing immune-related SD (irSD). In Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab), 6 out of 15 response evaluable subjects had an objective response rate by mWHO (40%; 1 CR (7%), 5 PRs (33%) with 2 additional uPRs (13%) and 2 irSDs and 1 irPR). In Cohort 3 (3 mg/kg nivolumab + 3 mg/kg ipilimumab), 3 out of 6 evaluable subjects had an objective response by mWHO (50%; 3 PRs (50%) with 1 additional irPR and 1 irSD.

Preliminary analysis revealed 16 of the 52 evaluable subjects (31%) had > 80% reduction in the size of target tumor lesions by the week 12 evaluation. This is compared to < 2% for 3 mg/kg ipilimumab monotherapy based on CA184020 (N=540) and < 3% for nivolumab monotherapy based on CA209003 (N=94, 0.1-10 mg/kg).

1.4.3.4 Clinical Pharmacology Summary

Ipilimumab Monotherapy

Ipilimumab has a terminal half life of approximately 15.4 days. The expected in vivo degradation of monoclonal antibodies is to small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes.

The population PK of ipilimumab was studied with 785 subjects and demonstrated that PK of ipilimumab is linear and exposures are dose proportional across the tested dose range of 0.3 to 10 mg/kg, and the model parameters are time invariant. Upon repeated dosing of ipilimumab, administered every three weeks, minimal systemic accumulation was observed by an accumulation index of 1.5-fold or less and ipilimumab steady-state concentrations were achieved by the third dose. The ipilimumab clearance of 16.8 mL/h from population PK analysis is consistent with that determined by PK analysis. The terminal half-life (T-HALF) and Vss of ipilimumab calculated from the model were 15.4 days, and 7.47 L, which are consistent with that determined by non-compartmental analysis (NCA). Volume of central (Vc) and peripheral compartment were found to be 4.35 L and 3.28 L, respectively, suggesting that ipilimumab first distributes into plasma volume and subsequently into extracellular fluid space. Clearance of ipilimumab and Vc were found to increase with increase in body weight. Nevertheless, there was no significant increase in exposure with increase in body weight when dosed on a mg/kg basis,

supporting dosing of ipilimumab based on a weight normalized regimen. Additional details are provided in investigator brochure.

Nivolumab Monotherapy

Single-dose pharmacokinetics (PK) of nivolumab was evaluated in subjects with multiple tumor types in MD1106-01 whereas multiple dose PK is evaluated in subjects in CA209003. In addition, a preliminary population pharmacokinetic (PPK) model has been developed with data from ± 350 subjects from MDX1106-01, MDX1106-02 and CA209003.

Single-dose PK of nivolumab was evaluated in 39 subjects with multiple tumor types in study MDX1106-01 in the dose range of 0.3 to 10 mg/kg. The median Tmax across single doses ranged from 1.6 to 3 hours with individual values ranging from 0.9 to 7 hours. The PK of nivolumab is linear in the range of 0.3 to 10 mg/kg with dose proportional increase in Cmax and AUC(INF) with low to moderate inter-subject variability observed at each dose level (ie, CV ranging from 7 to 45%). Geometric mean clearance (CL) after a single intravenous (IV) dose ranged from 0.13 to 0.19 mL/h/kg, while mean volume of distribution (Vz) varied between 83 to 113 mL/kg across doses. The mean terminal T-HALF of nivolumab is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of nivolumab may be similar to IgG4. Both elimination and distribution of nivolumab appear to be independent of dose in the dose range studied. Additional details are provided in the Investigator Brochure.

A preliminary PPK model was developed by nonlinear mixed effect modeling using data from 350 subjects from MDX1106-01, MDX1106-02 and CA209003. The body weight normalized dosing produces approximately constant trough concentrations over a wide range of body weight, and hence is appropriate for future clinical trials of nivolumab. Clearance of nivolumab is similar in all tumor types studied and is independent of dose range studied (0.1 to 10 mg/kg).

1.4.4 Rationale for CA209067 Study Design

1.4.4.1 Rationale for the use of ipilimumab as a Comparator

Ipilimumab was chosen as the comparator because it is the only FDA approved treatment of previously untreated, unresectable or metastatic melanoma without restriction to BRAF status that has demonstrated overall survival benefit in a Phase 3 randomized trial. In a retrospective analysis of a Phase 2 ipilimumab clinical trial in unresectable and metastatic melanoma, CA184004, rates of objective responses and stable disease in patients with BRAF-V600E mutation positive tumors were comparable to those in patients with the wildtype gene.[45] The schedule and dose of 3 mg/kg ipilimumab every 3 weeks for a total of 4 doses is based on the FDA and EMA prescribing information, recognizing that the EMA approved ipilimumab treatment is in pretreated unresectable or metastatic melanoma patients.[46,47]

1.4.4.2 Rationale for Nivolumab as an Experimental Arm and the Dose and Schedule for Nivolumab

Nivolumab monotherapy was chosen as one of the experimental arms because of a favorable risk-benefit ratio as seen in the large Phase 1 CA209003. The dose and schedule of nivolumab in this study will be 3 mg/kg every two weeks, based upon the analyses of safety, efficacy, and exposure-response data from the ongoing Phase 1 study CA209003. Anti-tumor activity was observed at dose levels ranging from 1 to 10 mg/kg in melanoma, NSCLC, and RCC, as well as at dose levels of 0.1 and 0.3 mg/kg in melanoma. The anti-tumor activity of nivolumab in RCC was investigated at dose levels 1 and 10 mg/kg, with the higher activity observed at 10 mg/kg. The observed anti-tumor activity in melanoma, and NSCLC was highest at 3 mg/kg, suggesting that anti-tumor activity approaches a plateau at dose levels of 3 mg/kg and above. Consistent with these observations, the results of the exposure-response analyses for these tumor types show that the probability of a tumor response tended to approach a plateau for trough concentrations produced by 3 and 10 mg/kg every 2 week dosing.

Nivolumab was adequately tolerated up to 10 mg/kg, the highest dose level tested, and no maximum tolerated dose (MTD) was identified. Although the spectrum, frequency, and severity of nivolumab-related AEs were generally similar across the dose levels tested, the 10 mg/kg doses level had numerically higher Grade 3/4 drug-related SAEs and AEs leading to discontinuation. Based upon the totality of the safety, efficacy, and exposure-response data, a dose of 3 mg/kg Q2W was selected as the dose anticipated to achieve an appropriate balance of efficacy and risk.

1.4.4.3 Rationale for Nivolumab combined with Ipilimumab as an Experimental Arm and the Dose and Schedule

The combination of nivolumab and ipilimumab was chosen as an experimental arm because of preclinical and preliminary clinical evidence suggesting synergy between nivolumab and ipilimumab. While PD-1 and CTLA-4 are both co-inhibitory molecules, evidence suggests that they use distinct mechanisms to limit T cell activation. Preliminary indirect data from peripheral T cell assessments suggest that a given T-cell checkpoint inhibitor may modulate host immune cell phenotype rendering them more susceptible to alternate checkpoint inhibitors and thereby enhancing anti-tumor activity. Specifically, nivolumab increased peripheral CTLA-4+ and regulatory T cells in subjects without clinical response in CA209006.[48] In a preclinical melanoma model, anti-CTLA-4 therapy increased PD-1+, PD-L1+ and CTLA-4+ tumor infiltrating T cells.[49] In addition, in the Phase 2 ipilimumab monotherapy study CA184004, increases in tumor infiltrating lymphocytes (TILs) and interferon-γ-inducible genes were observed following treatment with ipilimumab, and PD-L1 positive tumor cells co-localize with both TILs and interferon-γ expression in metastatic melanoma.[50, 51, 52]

The preliminary clinical evidence has demonstrated a higher frequency of patients with substantial tumor burden reduction for the combination of nivolumab and ipilimumab. Improved overall survival associated with substantial tumor burden reduction has been noted with immunotherapies. For instance, improved overall survival has been noted in metastatic

melanoma subjects obtaining a complete response to IL-2.[53] If this observation is also applicable to treatment with nivolumab combined with ipilimumab then there could also be the potential for large improvements in overall survival compared to ipilimumab.

Dose and Schedule Rationale

In CA209004, the 3 mg/kg nivolumab and 3 mg/kg ipilimumab cohort exceeded the maximum tolerated dose per protocol. In CA209004, while both Cohort 2 (1 mg/kg nivolumab + 3 mg/kg ipilimumab) and Cohort 2a (3 mg/kg nivolumab + 1 mg/kg ipilimumab) had similar clinical activity, a dose of 3 mg/kg of ipilimumab every 3 weeks for a total of four doses and 1 mg/kg nivolumab every 3 weeks for four doses followed by nivolumab 3mg/kg every 2 weeks until progression was chosen. Exposure-response analysis of nivolumab monotherapy across dose ranges of 1 mg/kg to 10 mg/kg reveals similar clinical activity while exposure-response analysis of 0.3 mg/kg, 3 mg/kg, and 10 mg/kg of ipilimumab monotherapy have demonstrated increasing activity with increase in dose in the phase 2 study CA184022.[54] Therefore, theoretically the selection of 3 mg/kg of ipilimumab (Cohort 2) may be more clinically impactful than selection of 3 mg/kg of nivolumab (Cohort 2a). In addition, by selecting the 3 mg/kg of ipilimumab allows the nivolumab contribution to the clinical efficacy of the combination arm to be determined because the same ipilimumab dose and schedule is utilized in both the combination arm and the ipilimumab monotherapy comparator arm.

The combination arm has a similar dose and schedule as that in CA209004 for the first 12 weeks, increasing the likelihood of replicating the clinical activity seen in the CA209004 study. Based on the clinical activity in CA209004, the majority of responses to the combination of nivolumab and ipilimumab occur in the first 12 weeks. Given the uncertainty of whether the ipilimumab administered past week 12 contributes to the clinical benefit and the fact that the approved schedule for ipilimumab is every 3 weeks for a total of four doses in the FDA and EMA approved label dosing section, ipilimumab will only be administered every 3 weeks for a total of 4 doses. Nivolumab monotherapy treatment every two weeks until progression was studied in CA209003 and is implemented program-wide across the nivolumab monotherapy Phase 3 registrational trials. Thus starting at week 12, which is after the completion of the four doses of combined nivolumab and ipilimumab, nivolumab would continue to be administered every two weeks until progression in order to maintain consistency with the nivolumab monotherapy program.

1.4.4.4 Rationale for Blinding

The study will be double-blinded in order to minimize bias arising from differences in treatment schedules, thresholds for classification of progression between the arms which could subsequently affect treatment duration between the arms and have an impact on the primary endpoint of overall survival, in addition to bias in reporting, classification, and management of adverse events. Subjects that have progressed and discontinued treatment will require knowledge of which treatment arm they were assigned to in order to appropriately select any post-progression subsequent therapy. For instance, subjects that have progressed and discontinued treatment will request unblinding to prevent retreatment with ipilimumab if they

had already progressed on the ipilimumab monotherapy arm. Therefore, upon progression of disease and treatment discontinuation of each subject, investigators will be unblinded to each subject's treatment assignment via the IVRS to inform the appropriate subsequent treatment; the Sponsor's central protocol team (including but not limited to clinical, statistics, data management) will remain blinded to treatment assignment.

1.4.4.5 Rationale for Unblinding

Treatment assignments of all subjects were unblinded to investigators after completion of the primary efficacy analysis and unblinding of the study within BMS. Sites were informed of the treatment assignment for all subjects.

For subjects in the unblinded portion of the study, the following applies:

1. Arm A and Arm B subjects should continue to be treated and monitored as specified in the protocol.
2. Arm C subjects are no longer required to perform the placebo infusions. These subjects will continue to be followed for safety and progression of disease. They will continue to complete their safety labs and tumors scans per protocol.

1.4.4.6 Rationale for Permitting Continued Treatment in Select Cases of Progressive Disease

Accumulating clinical evidence indicates some subjects treated with immune system stimulating agents may develop progression of disease (by conventional response criteria) before demonstrating clinical objective responses and/or stable disease. This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab and also with ipilimumab monotherapy.[55] Two hypotheses have been put forth to explain this phenomenon. First, enhanced inflammation within tumors could lead to an increase in tumor size which would appear as enlarged index lesions and as newly visible small non-index lesions. Over time, both the malignant and inflammatory portions of the mass may then decrease leading to overt signs of clinical improvement. Alternatively, in some individuals, the kinetics of tumor growth may initially outpace anti-tumor immune activity. With sufficient time, the anti-tumor activity will dominate and become clinically apparent. Therefore, subjects will be allowed to continue study therapy after initial investigator-assessed RECIST 1.1 defined progression if they are assessed to be deriving clinical benefit and tolerating study drug (Section 4.3.7). Such subjects must discontinue study therapy upon evidence of further progression.

1.4.4.7 Rationale for Progression Free Survival as a co-primary endpoint

The co-primary endpoint of the study is to compare the progression free survival and overall survival of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. Treatment options that are clinically active (eg, ipilimumab, vemurafenib, dabrafenib, trametinib) are increasingly available in subjects with

unresectable or metastatic melanoma. Progression free survival is not confounded by post-study drug therapies and has been demonstrated to correlate with overall survival in a meta-analysis of randomized, dacarbazine-controlled trials in metastatic melanoma.[56] In addition progression free survival has been accepted as an acceptable regulatory endpoint. Dabrafenib and trametinib as monotherapy and in combination was approved by the FDA for treatment of unresectable or metastatic melanoma based on Phase 3 clinical trials where the primary endpoint was progression free survival.[57,58,59] Radiographic images will be collected for independent radiological review committee tumor assessment.

1.4.4.8 Rationale for evaluation of PD-L1 Expression as a Predictive Biomarker

PD-L1 is expressed by many tumor types and its expression has been noted to correlate with decreased immune system function and worse clinical prognosis. It is hypothesized that PD-L1 expression within the tumor microenvironment, either on tumor cells, macrophages or lymphocytes is a means of evading immune system detection and destruction. Still others postulate that PD-L1 expression on tumor cells is a surrogate for interferon-gamma release from neighboring activated T cells and thus portends a good prognosis for immunotherapy agents, and in particular, agents targeting the PD-1/PD-L1 axis. Preliminary data from two small retrospective analyses supports the latter hypothesis in metastatic melanoma. PD-L1 positive status was associated with improved OS, irrespective of treatment, relative to PD-L1 negative status in subjects with metastatic melanoma (n=56) (Taube et al, STM 2012). Similarly, objective responses to nivolumab were limited to subjects defined as PD-L1 positive in a subset of subjects from study CA209003 (n = 42), which included 18 melanoma subjects (Topalian et al, NEJM 2012). In both of these studies, a prototype immunohistochemistry (IHC) assay was used and PD-L1 positive status was defined as ≥ 5% tumor cell membrane staining within a tumor tissue sample.

Based on these initial data, the sponsor is in the process of developing a reproducible diagnostic IHC assay that can be used to measure PD-L1 expression in tumor tissue. Using the verified version of the diagnostic assay, the sponsor has assessed additional tumor biopsy specimens from 38 CA209003 melanoma subjects for PD-L1 expression. Using a cutoff of 5% tumor cell membrane staining, 45% of subjects were defined as PD-L1 positive, consistent with the rate previously reported by Taube et al (STM 2012) at 45% (24/56 subjects) in metastatic melanoma.

With this verified version of the assay, an ORR of 44% (7/16) was observed in subjects with ≥ 5% tumor-cell positivity and 17% (3/18) in subjects with < 5 % tumor cell positivity.

The limited preliminary evidence suggests that PD-L1 expression may be a prognostic marker that may also predict for nivolumab clinical activity. Therefore, one of the stratification factors will be PD-L1 expression status, in order to minimize the potential for imbalances in PD-L1 expression across treatment arms when assessing the potential prognostic and/or predictive role of this marker for overall survival.

1.4.4.9 Rationale for Quality of Life Evaluation

Evaluating quality of life (QoL) in oncology clinical studies is becoming increasingly important to understand the impact of benefit/risk from the patient perspective, and for quality of life adjustments for survival data used in economic models. The EORTC QLQ C-30 will be used to assess changes in QoL during and after treatment in the different arms of the study. The EQ-5D will be used to assess general health status and the data will be used to calculate utilities for use in economic models. The WPAI questionnaire for measure of work and activity impairment exhibits strong validity and reliability, plus the ability to present the results on impairment in financial terms. Employers are increasingly concerned about the burden of illness in their workforce and its financial impact. The melanoma population is younger than in many other cancers and effective treatment can improve productivity in the surviving patients. Additionally, some decision makers may want assurance that all cost implications have been considered. The costs of lost productivity, in addition to standard direct healthcare costs are increasingly required to meet requirements for a broader societal perspective that some health authorities request. The cost of lost productivity as measured by the WPAI will as a result be implemented into the economic model of nivolumab.

With the emergence of patients that experience long-term survival with immunotherapies, payers, physicians and patients are beginning to question not only about the duration of survival (OS) but also the quality of survival after treatment discontinuation. For the long term follow up, the EQ-5D-VAS will be utilized to assess quality of survival. Post- progression, patients that have received nivolumab therapy may live longer and have a better QoL than those that did not.

1.5 Overall Risk/Benefit Assessment

There continues to be a significant unmet need for patients with previously untreated, unresectable or metastatic melanoma.

Nivolumab monotherapy has demonstrated clinical activity across several tumor types, including advanced prior treated melanoma, with objective response rates of 20 - 41% in 106 melanoma subjects treated at various dose levels in CA209003. Nivolumab has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea.

The combination of nivolumab and ipilimumab has the potential for increased benefit compared to both ipilimumab monotherapy and nivolumab monotherapy. Preliminary analysis of the evaluable CA209004 subjects revealed that approximately 33% of the subjects had >80% tumor reductions in target lesions by week 12. This compares favorably to < 2% for 3 mg/kg ipilimumab monotherapy based on the CA184020 (N=540) and <3% for nivolumab monotherapy based on the CA209003. However, the combination of nivolumab and ipilimumab also has the potential for increased frequencies of adverse events. The most common (reported at > 10% incidence) treatment related AEs are fatigue, rash, pruritus, diarrhea, lipase increased, pyrexia, ALT increase, AST increased, amylase increased and vitiligo. Although the preliminary data suggests an increase in adverse event frequency of nivolumab combined with ipilimumab compared to ipilimumab monotherapy or nivolumab monotherapy, there were no

unexpected adverse events noted in the combination of nivolumab and ipilimumab. In addition, many of the Grade 3-4 adverse events associated with the nivolumab combined with ipilimumab were laboratory in nature, without clinical sequalae and adverse events have been manageable and reversible following intervention dose delays or with systemic steroid treatment.

Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on the individual risk-benefit ratio. The robust clinical activity demonstrated by nivolumab monotherapy and the promising clinical activity of nivolumab combined with ipilimumab in subjects with advanced melanoma in combination with the manageable safety profile and the lack of approved survival-prolonging agents for a large segment of the previously untreated population supports the further development of nivolumab and nivolumab combined with ipilimumab in subjects with previously untreated, unresectable or metastatic melanoma.

2 ETHICAL CONSIDERATIONS

2.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol and any amendments and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion prior to initiation of the study.

All potential serious breaches must be reported to BMS immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

2.2 Institutional Review Board/Independent Ethics Committee

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials (eg, advertisements), and any other written information to be provided to subjects. The investigator or BMS should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects and any updates.

The investigator or BMS should provide the IRB/IEC with reports, updates and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

2.3 Informed Consent

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

In situations where consent cannot be given to subjects, their legally acceptable representatives are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which the subject volunteers to participate.

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

Investigators must:

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.

Subjects unable to give their written consent (eg, stroke or subjects with or severe dementia) may only be enrolled in the study with the consent of a legally acceptable representative. The subject must also be informed about the nature of the study to the extent compatible with his or her understanding, and should this subject become capable, he or she should personally sign and date the consent form as soon as possible. The explicit wish of a subject who is unable to give his or her written consent, but who is capable of forming an opinion and assessing information to refuse participation in, or to be withdrawn from, the clinical study at any time should be considered by the investigator.

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

3 INVESTIGATIONAL PLAN

3.1 Study Design and Duration

This is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable or metastatic Stage III or stage IV melanoma, as per the AJCC staging system, and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization.

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

- PD-L1 status
  - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- BRAF status
  - BRAF V600 mutation positive vs
  - BRAF V600 wildtype
- AJCC M stage at screening (See Appendix 3)
  - M0/M1a/M1b vs
  - M1c

Subjects will be treated in a blinded fashion with one of the following:

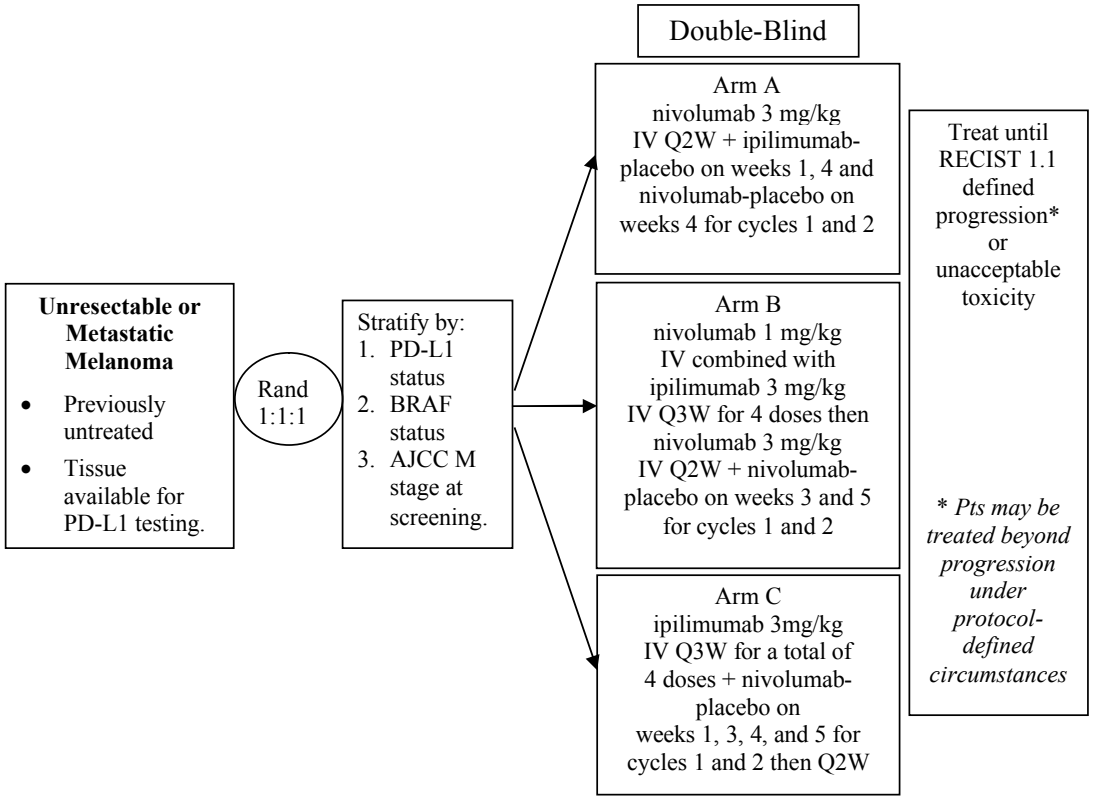
- Arm A: nivolumab 3 mg/kg IV Q2W + ipilimumab-placebo on weeks 1, 4 and nivolumab-placebo on weeks 4 for cycles 1 and 2
- Arm B: nivolumab 1 mg/kg IV combined with ipilimumab 3 mg/kg IV Q3W for 4 doses then nivolumab 3 mg/kg IV Q2W + nivolumab-placebo on weeks 3 and 5 for cycles 1 and 2.
- Arm C: ipilimumab 3 mg/kg IV Q3W for a total of 4 doses + nivolumab-placebo on weeks 1, 3, 4 and 5 for cycles 1 and 2 then Q2W

Depending on the treatment arm, the subject will receive a placebo; nivolumab-placebo or ipilimumab-placebo that closely matches either nivolumab or ipilimumab, respectively. The placebos are administered as per the dosing guidelines of the matching drug. The schedule of placebo administration will depend on the treatment arm. See Table 4.3-1 and Table 4.3-2. Note that, in the unblinded portion of the study, per Amendment 11, subjects in Arm C will no longer receive nivolumab-placebo infusions, but will enter the follow-up phase.

One cycle of treatment will be defined as six weeks. Dose reductions will be not be allowed for any of the treatments. On-study tumor assessments will begin 12 weeks from randomization and will continue every 6 weeks up to week 49 and every 12 weeks thereafter until disease progression or treatment discontinuation, whichever occurs later. Treatment beyond initial investigator-assessed RECIST 1.1-defined progression is permitted if the subject has investigator-assessed clinical benefit and is tolerating study drug.

The study design schematic is presented in Figure 3.1-1

Figure 3.1-1: Study Design Schematic



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

Screening Phase:

- Begins by establishing the subject's initial eligibility and signing of the informed consent form (ICF).
- Subject is enrolled using the Interactive Voice Response System (IVRS).
- Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses

Treatment Phase:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to either the nivolumab + placebo arm (Arm A), the nivolumab + ipilimumab arm (Arm B) or the ipilimumab + placebo arm (Arm C).
- A negative pregnancy test should be documented within 24 hours prior to the start of investigational product.

PRO (Patient Reported Outcome) instruments must be completed after randomization, prior to the first dose of study therapy and according to the schedule in Table 5.1-2.

- Within 3 days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1).
- On-study laboratory assessments should be drawn within 72 hours prior to dosing.
- Adverse event assessments should be documented at each clinic visit. WOCBP must have a pregnancy test during week 1 and week 4 for cycles 1-2 and week 1 and week 5 of starting from cycle 3. Table 5.1-2 and Table 5.1-3
- PK samples and immunogenicity samples will be collected according to the schedule in Table 5.5-1
- Study drug dosing may be delayed for toxicity. See Section 4.3.2

For the first 2 cycles (12 weeks);

- In subjects on the nivolumab + placebo arm (Arm A), nivolumab is administered every 2 weeks for 6 doses + placebo Table 4.3-1
- In subjects on the nivolumab combined with ipilimumab arm (Arm B), nivolumab and ipilimumab are administered every 3 weeks for 4 doses + placebo Table 4.3-1
- In subjects on the ipilimumab + placebo arm (Arm C), ipilimumab is administered every 3 weeks for 4 doses + placebo Table 4.3-1

Starting cycle 3;

- In subjects on the nivolumab + placebo arm (Arm A), nivolumab is administered every 2 weeks Table 4.3-2
- In subjects on the nivolumab combined with ipilimumab arm (Arm B), nivolumab is administered every 2 weeks Table 4.3-2
- In subjects on the ipilimumab + placebo arm (Arm C), placebo is administered every 2 weeks Table 4.3-2. Per Amendment 11, during the open-label portion of the study, placebo will no longer be administered and subjects will enter the follow-up phase.
- Study drug dose may be delayed for toxicity. See Section 4.3.2.
- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for the first 12 months, and then every 12 weeks (± 1 week) until disease progression or treatment discontinuation, whichever occurs later.
- This phase ends when the subject is discontinued from study therapy. For a complete list of reasons for treatment discontinuation, see Section 3.5.

Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).
- Two follow-up visits include collection of PK/immunogenicity samples Table 5.5-1.
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 12 weeks (± 1 week) after randomization and continuing every 6 weeks (± 1 week) for the first 12 months from randomization, and every 12 weeks (± 1 week) thereafter until documented tumor progression.
- During the blinded portion of the study, the subject's treatment assignment will be unblinded to the site for those subjects who have disease progression **and** have discontinued treatment.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All adverse events will be documented for a minimum of 100 days after last dose.
- After completion of the first two follow-up visits, subjects will be followed every 3 months for survival.

  Overall survival is a key endpoint of this study. Post study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study drug must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with section 3.1 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 as detailed in the Time and Events Table 5.1-4. Follow-up Assessments (CA209067). 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.

PRO instruments will be completed according to the schedule in Table 5.1-4.

The total duration of the study from start of randomization to final analysis of OS is expected to be 36 months (8 months of accrual + 28 months of follow-up), assuming a piecewise accrual rate (30 subjects during Months 1 and 2, 75 subjects during Month 3, 120 subjects during Month 4, 150 subjects during Month 5, 375 subjects during Month 6, 45 subjects during Month 7, and 90 subjects during Month 8). PFS will be analyzed prior to OS (Section 8.1). Additional survival follow-up may continue for up to 5 years from the primary analysis of survival. The study will end once survival follow-up has concluded.

3.2 Post Study Access to Therapy

At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of BMS. BMS reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market.

3.3 Study Population

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

3.3.1 Inclusion Criteria

1. Signed Written Informed Consent

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

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

2. Target Population

a) Histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system.

b) Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1 (Refer to Appendix 2)

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

d) Measurable disease by CT or MRI per RECIST 1.1 criteria section 5.4.3.1

e) Tumor tissue from an unresectable or metastatic site of disease must be provided for biomarker analyses. In order to be randomized, a subject must be classified as PD-L1 positive, PD-L1 negative, or PD-L1 indeterminate. If an insufficient amount of tumor tissue from an unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of additional tumor tissue for performance of biomarker analyses.

f) Subjects must have known BRAF V600 mutation status or consent to BRAF V600 mutation testing per local institutional standards during the Screening Period

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

h) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:

i) WBC ≥ 2000/µL

ii) Neutrophils ≥ 1500/µL

iii) Platelets ≥ 100 x10^3/µL

iv) Hemoglobin > 9.0 g/dL

v) Serum creatinine ≤ 1.5 x ULN or creatinine clearance (CrCl) ≥ 40 mL/min (using the Cockcroft-Gault formula):

$$\text{Female CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\text{Male CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

vi) AST/ALT ≤ 3 x ULN

vii) Total Bilirubin ≤ 1.5 x ULN (except subjects with Gilbert Syndrome, who can 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 pre-treatment failure (ie, subject has not been randomized / has not been treated) after obtaining agreement from the medical monitor prior to re-enrolling a subject. If re-enrolled, the subject must be re-consented.

3. Age and Reproductive Status

a) Men and women, ≥ 18 years of age

b) Women of childbearing potential (WOCBP) must use method(s) of contraception as indicated in Appendix 5. For a teratogenic study drug and/or when there is insufficient information to assess teratogenicity (preclinical studies have not been done), a highly effective method(s) of contraception (failure rate of less than 1% per year) is required. The individual methods of contraception and duration should be determined in consultation with the investigator. WOCBP must follow instructions for birth control of

the investigational drug greater than 24 hours, contraception should be continued for a period of 30 days plus the time required for the investigational drug to undergo five half lives. WOCBP should therefore use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for nivolumab) after the last dose of investigational drug.

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

d) Women must not be breastfeeding

e) Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year The investigator shall review contraception methods and the time period that contraception must be followed. Men that are sexually active with WOCBP must follow instructions for birth control when the half life of the investigational drug is greater than 24 hours, contraception should be continued for a period of 90 days plus the time required for the investigational drug to undergo five half lives. Men who are sexually active with WOCBP must continue contraception for 7 months after the last dose of investigational drug.

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

3.3.2 Exclusion Criteria

1. Target Disease Exceptions

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

b) Ocular melanoma

2. Medical History and Concurrent Diseases

a) Any participation in a blinded Phase 3 ipilimumab trial

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

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

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

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

f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.

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 allergy to study drug components.

b) History of severe hypersensitivity reaction to any monoclonal antibody.

5. Sex and Reproductive Status

a) WOCBP who are pregnant or breastfeeding

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

6. Other Exclusion Criteria

a) Prisoners or subjects who are involuntarily incarcerated

b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness

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

3.3.3 Women of Childbearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 in the absence of other biological or physiological causes.

In additional, women under the age of 62 must have a documented serum follicle stimulating hormone, (FSH) level > 40mIU/mL.

3.4 Concomitant Treatments

3.4.1 Prohibited and/or Restricted Treatments

The following medications are prohibited during the study:

- Immunosuppressive agents (except to treat a drug-related adverse event)
- Systemic corticosteroids > 10 mg daily prednisone equivalent (except as stated in Section 3.4.4 or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, radiation therapy except for palliative radiation therapy described in Section 3.4.2.1, or standard or investigational agents for treatment of cancer).

Supportive care for disease-related symptoms may be offered to all subjects on the trial.

3.4.2 Other Restrictions and Precautions

3.4.2.1 Palliative Therapy

Palliative (limited-field) radiation therapy and palliative surgical resection are permitted if the following criteria are met:

1. The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression (Section 4.3.7).
2. The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record.

3.4.3 Surgical Resection Following initial Response

Investigators may choose to resect solitary lesions in patients with unresectable or metastatic melanoma and render the patient free of macroscopic disease. Subjects enrolled in this study may have lesions surgically resected only following consultation with the Medical Monitor and following the Week 18 re-staging assessments. If tumor shrinkage of the solitary lesion is noted on the re-staging assessment (eg, Week 18), it is highly encouraged that surgical resection be delayed until subsequent scans fail to demonstrate further shrinkage. Patients with a PR who go on to have surgical resection of remaining disease will be considered a PR. Tumor tissue of any resected solitary lesion should be submitted to BMS (see section 5.6.1.) Detailed instructions of the obtaining, processing, labeling, handling, storage and shipment of these specimens will be provided in a separate Procedure Manual at the time of study initiation.

3.4.4 Permitted Therapy

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

Concomitant medications are recorded at baseline and throughout the treatment phase of the study in the appropriate section of the CRF. All medications (prescriptions or over the counter medications) continued at the start of the study or started during the study and different from the study drug must be documented in the concomitant therapy section of the CRF.

3.5 Discontinuation of Subjects from Treatment

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

- Subject's request to stop study treatment
- Any clinical adverse event (AE), laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
- Pregnancy
- Termination of the study by Bristol-Myers Squibb (BMS)
- Loss of ability to freely provide consent through imprisonment or involuntarily incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness
- Additional protocol specified reasons for discontinuation (see Section 4.3.5)

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

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

3.6 Post Treatment Study Follow up

In this study, overall survival is a key endpoint of the study. Post treatment study follow-up is of critical importance and is essential to preserving subject safety and the integrity of the study. Subjects who discontinue study treatment must continue to be followed for collection of outcome and/or survival follow-up data as required and in line with Section 5 Study Assessments and Procedures until death or the conclusion of the study.

3.6.1 Withdrawal of Consent

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

3.6.2 Lost to Follow-Up

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

If investigator's use of third-party representative to assist in the follow-up portion of the study has been included in the subject's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining subject's contact information or other public vital status data necessary to complete the follow-up portion of the study. If after all attempts, the subject remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the subject's medical records.

4 TREATMENTS

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

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

4.1 Study Treatments

Table 4.1-1: Product Description: Treatment Period

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Secondary Packaging (Qty) /Label Type	Appearance	Storage Conditions (per label)
BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial/ Open-label	10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect form light and freezing
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial/Open-label	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

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

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 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.

4.1.1 Investigational Product

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

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

In this protocol, investigational product(s) is/are: BMS-936558 (nivolumab), ipilimumab, nivolumab-placebo (0.9% Sodium Chloride Injection) and ipilimumab-placebo (0.9% Sodium Chloride Injection or 5% Dextrose Injection).

4.1.2 Non-investigational Product

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

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

4.1.3 Handling and Dispensing

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

Investigational product documentation must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

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

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

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for BMS-936558 (nivolumab) and ipilimumab.

Nivolumab (BMS-936558)

Nivolumab (BMS-936558) vials must be stored at a temperature of 2°C to 8°C and should be protected from light and freezing. If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions" and/or pharmacy reference sheets.

Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyolefin bags have been observed.

Nivolumab or Nivolumab-Placebo is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/0.22 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/ml. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab

Ipilimumab injection can be used for IV administration without dilution after transferring to a PVC (polyvinyl chloride), non-PVC/non-DEHP (di-(2-ethylhexyl)phthalate) or glass containers and is stable for 24 hours at 2-8ºC or room temperature/room light (RT/RL). For ipilimumab storage instructions, refer to ipilimumab IB and/or pharmacy reference sheets.

Recommended safety measures for preparation and handling include protective clothing, gloves, and safety cabinets.

The same storage and use conditions recommended for product also apply to the placebo for Ipilimumab Injection.

Ipilimumab or Ipilimumab-Placebo is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2 to 1.2 micron in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline or 5% Dextrose Injection to concentrations between 1 mg/mL and 4 mg/mL. It is not to be administered as an IV push or bolus injection. Care must be taken to assure sterility of the prepared solutions, since the drug product does not contain any antimicrobial preservatives or bacteriostatic agents. At the end of the infusion, flush the line with a sufficient quantity of normal saline or 5% dextrose solution.

When both study drugs are to be administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion.

4.2 Method of Assigning Subject Identification

CA209067 (CheckMate 067) is a randomized, double-blind study. After the subject's initial eligibility is established and informed consent has been obtained, the subject must be enrolled into the study by calling an interactive voice response system (IVRS) to obtain the subject number. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document. The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

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

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

- Subject number
- Date of birth
- PD-L1 status (PD-L1 positive vs PD-L1 negative/indeterminate) entered by vendor
- BRAF V600 mutational status
- M Stage at screening (see Appendix 3)

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

- PD-L1 status
  - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- M Stage at screening(see Appendix 3)
  - M0/M1a/M1b vs
  - M1c
- BRAF V600 mutational status
  - Wild type vs
  - Mutation positive

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

4.3 Selection and Timing of Dose for Each Subject

Dosing schedule for all three arms is detailed in Table 4.3-1 and Table 4.3-2.

Table 4.3-1: Dosing Schedule for Cycle 1 and Cycle 2

1 Cycle = 6 weeks						
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**
Arm A (Nivolumab Monotherapy 3mg/kg + Placebo)	3mg/kg Nivolumab 3 mg/kg Ipilimumab-Placebo		3 mg/kg Nivolumab	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab-Placebo	3 mg/kg Nivolumab	
Arm B (Nivolumab 1mg/kg + Ipilimumab 3 mg/kg)	1 mg/kg Nivolumab [a] 3 mg/kg Ipilimumab		3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab[a], 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	
Arm C (Ipilimumab Monotherapy 3mg/kg+ Placebo)	3 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab		3 mg/kg Nivolumab-Placebo	1 mg/kg Nivolumab-Placebo 3 mg/kg Ipilimumab	3 mg/kg Nivolumab-Placebo	

[a] Arm B - In order to protect the blind, the 1mg/kg nivolumab administered on D1W1 and D1W4 in cycles 1 and 2 should be diluted to the same volume as 3 mg/kg nivolumab-placebo prepared on D1W3, D1W5 and treatment visits after Cycle 2.

Table 4.3-2: Dosing Schedule Cycle 3 and Beyond

1 Cycle = 6 weeks						
	Day 1 Week 1	**Day 1 Week 2**	**Day 1 Week 3**	**Day 1 Week 4**	**Day 1 Week 5**	**Day 1 Week 6**
Arm A (Nivolumab Monotherapy + Placebo)	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	
Arm B (Nivolumab + Ipilimumab)	3 mg/kg Nivolumab		3 mg/kg Nivolumab		3 mg/kg Nivolumab	
Arm C (Ipilimumab Monotherapy + Placebo)[a]	3 mg/kg Nivolumab-Placebo		3 mg/kg Nivolumab-Placebo		3 mg/kg Nivolumab-Placebo	

[a] Per Amendment 11, all participants treated with placebo during the blinded portion of the study will no longer receive placebo infusions during the unblinded portion of the study and will enter the follow-up phase.

First dose to be administered within 3 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 nivo-placebo infusion.

Ipilimumab or ipilimumab-placebo may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution. Nivolumab or nivolumab-placebo may be diluted in 0.9% Sodium Chloride Solution.

The dosing calculations should be based on the body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard. There will be no dose modifications allowed.

During cycles 1 and 2

- subjects may be dosed no less than 12 days between
  - C1W1 and C1W3
  - C1W5 and C2W1
  - C2W1 and C2W3
- subjects may be dosed no less than 5 days between
  - C1W3 and C1W4
  - C1W4 and C1W5
  - C2W3 and C2W4
  - C2W4 and C2W5

Starting from cycle 3, subjects may be dosed no less than 12 days from the previous dose of drug.

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

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

4.3.1 Antiemetic Premedications

Antiemetic premedications should not be routinely administered prior to dosing of drugs. See section 4.3.6 for premedication recommendations following a nivolumab or ipilimumab related infusion reaction.

4.3.2 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab, or both). All study drugs must be delayed until treatment can resume (see Section 4.3.4.)

Dose delay criteria also apply for the placebo version of each agent, given the blinded nature of this study.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
  - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the BMS Medical Monitor for Grade 3 amylase or lipase abnormalities.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

4.3.2.1 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
- Neurological

While the ipilimumab investigator brochure contains safety management algorithms for similar adverse events, the recommendations are to follow the nivolumab algorithms for immune-oncology agents (I-O) in order to standardize the safety management across the three blinded treatment arms.[60]

Therefore, the algorithms recommended for utilization in CA209067 are included in Appendix 4.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider recommendations provided in Section 1.4.3.2 Summary of Safety - Adverse Event Management Algorithms.

4.3.3 Dose Modifications

Dose reductions or dose escalations are not permitted.

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

4.3.4 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 delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 4.3.5)should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

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

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.

4.3.5 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 the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for 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
- 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
- Any dosing interruption lasting > 6 weeks with the following exceptions:
  - Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
  - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the BMS medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab or ipilimumab dosing.

4.3.6 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 NCI CTCAE (version 4.0) guidelines.

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

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

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

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

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

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

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

4.3.7 Treatment Beyond Disease Progression

As described in Section 1.5 accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.[61]

During the blinded portion of the study, subjects will be permitted to continue Arm A, B, or C treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit
  and
- Subject is tolerating study drug.

During the unblinded portion of the study, subjects in Arm C who were receiving placebo infusions will not be permitted to continue Arm C treatment beyond initial RECIST 1.1 defined PD.

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

In order to assess a patient's current BRAF V600 mutational status at time of progression and make informed subsequent treatment decisions, an optional tumor biopsy at time of progression can be considered when assessing whether to treat beyond progression. As discussed in section 5.6.1the optional tumor biopsy may also be utilized to investigate potential mechanisms of resistance to immunotherapeutic agents and the impact of treatment on relevant melanoma biomarkers.

A portion of tumor tissue from a biopsy should be submitted to BMS. Detailed instructions of the labeling, handling, storage and shipment of these specimens will be provided in a separate procedure manual.

All decisions to continue treatment beyond initial progression must be discussed with the BMS Medical Monitor and documented in the study records. Subjects will be re-consented with an ICF describing any reasonably foreseeable risks or discomforts.

Subjects should discontinue study therapy upon further evidence of further progression, defined as an additional 10% or greater increase in tumor burden volume from time of initial progression (including all target lesions and new measurable lesions).

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

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

4.4 Blinding/Unblinding

4.4.1 Blinded Portion of the Study

During the blinded portion of the study, blinding of treatment assignment is critical to the integrity of this clinical study. 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 during the blinded portion of the study. The subject’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded during the blinded portion of the study.

Before breaking the blind of an individual subject's treatment during the blinded portion of the study, 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 during the blinded portion of the study be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind during the blinded portion of the study. The Principal Investigator should only call for emergency unblinding during the blinded portion of the study AFTER the decision to discontinue the subject has been made.

For subjects who are receiving treatment and have not progressed, the Sponsor, subjects, investigator and site staff will be blinded to the study drug administered (nivolumab + placebo or ipilimumab + placebo or nivolumab plus ipilimumab). Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned by sponsor to

provide oversight of drug supply and other unblinded study documentation. Upon progression of disease and treatment discontinuation of each subject, the investigator and subject will be unblinded to each subject's treatment assignment through the IVRS. The Sponsor's central protocol team (including but not limited to clinical, statistics, data management) will remain blinded. As of 24-Mar-2015, in accordance with the Data Monitoring Committee charter, the DMC allowed the unblinding of a limited number of sponsor personnel in order to enable the development of a clinical study report for the co-primary endpoint of progression free survival.

For this study, the method of unblinding is through the IVRS.

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

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

Any request to unblind a subject for non-emergency purposes during the blinded portion of the study should be discussed with the Medical Monitor.

The Sponsor will remain blinded until final PFS results are unblinded or until final analysis of the OS endpoint, whichever occurs first as described in the statistical analysis plan. Designated staff of Bristol-Myers Squibb Research & Development may be unblinded prior to database lock to facilitate the bioanalytical analysis of pharmacokinetic samples and immunogenicity. A bioanalytical scientist in the Bioanalytical Sciences department of Bristol-Myers Squibb Research & Development (or a designee in the external central bioanalytical laboratory) will be unblinded to the randomized treatment assignments in order to minimize unnecessary bioanalytical analysis of samples

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

4.4.2 Open-Label (Unblinded) Portion of the Study

For subjects in the unblinded portion of the study, the following applies:

1. Arm A and Arm B subjects should continue to be treated and monitored as specified in the protocol.
2. Arm C subjects are no longer required to perform the placebo infusions. These subjects will continue to be followed for safety and progression of disease. They will continue to complete their safety labs and tumors scans per protocol.

4.5 Treatment Compliance

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

4.6 Destruction and Return of Study Drug

4.6.1 Destruction of Study Drug

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

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

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

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

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

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

4.6.2 Return of Study Drug

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

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

5 STUDY ASSESSMENTS AND PROCEDURES

5.1 Flow Chart/Time and Events Schedule

Table 5.1-1: Screening Assessments (CA209067)

Procedure	Screening Visit	Notes
Eligibility Assessments		
Informed Consent	X	
Inclusion/Exclusion Criteria	X	All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization
Medical History	X	
Tumor Tissue Samples	X	Sufficient tumor tissue from an unresectable or metastatic site (block or minimum of 10 slides; obtained from core biopsy, punch biopsy, excisional biopsy or surgical specimen).
Safety Assessments		
Physical Examination	X	
Vital Signs and oxygen saturation	X	Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion. Obtain vital signs at the screening visit and within 72 hours prior to first dose
Physical Measurements (including performance status)	X	Height and weight
ECG	X	Within 14 days prior to randomization
Assessment of Signs and Symptoms	X	Within 14 days prior to randomization
Concomitant Medication Collection	X	Within 14 days prior to randomization
Laboratory Tests	X	CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, amylase, lipase, TSH, Free T4, Free T3, Hep B/C(HBV sAG, HCV antibody or HCV RNA), within 14 days prior to randomization
Pregnancy Test (WOCBP Only)	X	

Table 5.1-1: Screening Assessments (CA209067)

Procedure	Screening Visit	Notes
Efficacy Assessment		
Screening/Baseline Tumor Assessments	X	Chest, Abdomen, Pelvis and Brain and all other known sites of disease within 28 days prior to randomization

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)[a]

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Safety Assessments							
Targeted Physical Examination	X		X	X	X		To be performed only as clinically indicated within 72 hours prior to dosing.
Vital Signs and Oxygen Saturation	X		X	X	X		Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing.
Physical Measurements (including performance status)	X		X	X	X		Weight and ECOG status within 72 hours prior to dosing
Adverse Events Assessment	Continuously						
Review of Concomitant Medications	X		X	X	X		
Laboratory Tests	X			X			Within 72 hrs prior to dosing to include CBC w/ differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, Glucose, amylase, lipase, TSH (with reflexive Free T4 and Free T3)
Pregnancy Test (WOCBP Only)	X			X			Within 24 hours prior to administration of study drug. Serum or Urine
Immunogenicity blood sample	See Table 5.5-1 for details regarding specific sample timing						
Pharmacokinetic Samples							
PK samples	See Table 5.5-1 for details regarding specific sample timing						

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)[a]

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Exploratory Biomarker Testing							
Exploratory Serum Biomarkers	X		Y				To be collected pre-dose; Y= only for Cycle 1
Peripheral Blood RNA	X		Y				To be collected pre-dose; Y= only for Cycle 1
Peripheral Blood Mononuclear Cells (PBMCs)	X		Y				To be collected pre-dose; Y= only for Cycle 1
Whole Blood Sample (DNA)	Y						EDTA Tubes for DNA. Must be obtained prior to dosing. Y= only for Cycle 1.
Efficacy Assessments							
Tumor Assessments						Y	FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization. SUBSEQUENT tumor assessments should occur every 6 weeks (1 ± wk) until disease progression. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline. Y=Cycle 2 only
Clinical Drug Supplies							
IVRS-Randomize	Y						Y=Only for cycle 1

Table 5.1-2: On-study Assessments Cycles 1 and 2 Only (CA209067)[a]

Procedure	Cycle 1 and Cycle 2 (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Administer Study Treatment	X		X	X	X		First dose to be administered within 3 days following randomization. See section 4.3 Subsequent doses may be administered within 3 days after the scheduled date if necessary.
Outcomes Research Assessments							
EORTC QLQ C-30	X				X		D1W1 should be completed after randomization but prior to dosing
EQ-5D	X				X		D1W1 should be completed after randomization but prior to dosing
WPAI-GH	X				X		D1W1 should be completed after randomization but prior to dosing
Health Care Resource Utilization			X	X	X		Prior to dosing

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

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209067)[a]

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Safety Assessments							
Targeted Physical Examination	X		X		X		To be performed only if clinically indicated within 72 hours prior to dosing
Vital Signs and Oxygen Saturation	X		X		X		Including BP, HR, temperature and oxygen saturation by pulse oximetry. Pulse oximetry at rest and after exertion prior to dosing.
Physical Measurements (including performance status)	X		X		X		Weight and ECOG status within 72 hours prior to dosing.
Adverse Events Assessment	Continuously						
Review of Concomitant Medications	X		X		X		
Laboratory Tests	X				X		Within 72 hrs prior to re-dosing to include CBC w/ differential, LFTs, 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 (WOCBP Only)	X				X		Within 24 hours prior to administration of study drug. Serum or Urine
Immunogenicity blood sample	See **Table 5.5-1** for details regarding specific sample timing						
Pharmacokinetic Samples							
PK samples	See **Table 5.5-1** for details regarding specific sample timing						

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209067)[a]

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Efficacy Assessments							
Tumor Assessments						X	FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization. SUBSEQUENT tumor assessments should occur every 6 weeks (1± wk) up to week 49, then every 12 weeks until disease progression. For responders (CR, PR or SD) on study beyond 2 years, an extension of the frequency of scans from every 12 weeks to every 24 weeks until disease progression and treatment discontinuation, is permitted. Subjects who discontinue study therapy for reasons other than progression should continue to be scanned until progression is documented. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.
Clinical Drug Supplies							
Administer Study Treatment	X		X		X		Subsequent doses may be administered within 3 days after the scheduled date if necessary. See section 4.3. Per Amendment 11, subjects in Arm C in the unblinded portion of the study will stop placebo infusions and will enter the follow-up phase.

Table 5.1-3: On-study Assessments Cycle 3 and Beyond (CA209067)[a]

Procedure	Cycle 3 and Beyond (Cycle = 6 weeks)						Notes
	Day 1 Week 1	Day 1 Week 2	Day 1 Week 3	Day 1 Week 4	Day 1 Week 5	Day 1 Week 6	
Outcomes Research Assessments							
EORTC QLQ C-30	X				Y		Prior to dosing. Y=only during 1st 6 months
EQ-5D	X				Y		Prior to dosing. Y=only during 1st 6 months
WPAI-GH	X				Y		Prior to dosing. Y=only during 1st 6 months
Health Care Resource Utilization	X		X		X		Prior to dosing at every study drug administration visit.

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

Table 5.1-4: Follow-up Assessments (CA209067) - *All Subjects*

Procedure	Follow-Up[a], Visits 1 and 2	Survival[b], Follow-up Visits	Notes
Safety Assessments			
Targeted Physical Examination	X		To assess for potential late emergent study drug related issues
Adverse Events Assessment	X	X	
Laboratory Tests	X		On site/local CBC w/differential, LFTs, BUN, creatinine and TSH for X01, repeat at X02 if study drug related toxicity persists.
Pregnancy Test	X		Serum or urine
Review of Concomitant Medication	X		
Immunogenicity blood sample	X		Refer to Table 5.5-1 for details regarding specific sample timing
Outcomes Research Assessments			
EORTC QLQ C-30	X		Follow-up visits 1 and 2 only (ePRO)
EQ-5D	X	Y	X=entered by patient, Y=Instrument to be entered by site (ePRO) every 3 months for the first 12 months then every 6 months thereafter.
WPAI-GH	X		Follow-up visits 1 and 2 only (ePRO)
Health Care Resource Utilization	X		Follow-up visits 1 and 2 only
Survival Status			
Subject Status	X	X	Every 3 months, may be accomplished by visit or phone contact, to include subsequent anti-cancer therapy

Table 5.1-4: Follow-up Assessments (CA209067) - *All Subjects*

Procedure	Follow-Up[a], Visits 1 and 2	Survival[b], Follow-up Visits	Notes
Efficacy Assessments			
Tumor Assessments	X		Only for subjects without progression on study therapy. FIRST tumor assessment should first be performed at 12 weeks (± 1 wk) following randomization SUBSEQUENT tumor assessments should occur every 6 weeks (± 1 wk) thereafter for up to Week 49, then every 12 wks (± 1 wk) until disease progression For responders (CR, PR or SD) on study beyond 2 years, an extension of the frequency of scans from every 12 weeks to every 24 weeks until disease progression and treatment discontinuation, is permitted. Subjects who discontinue study therapy for reasons other than progression should continue to be scanned until progression is documented. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at screening/baseline.
Pharmacokinetic Samples			
	X		See Table 5.5-1 for schedule of assessments

[a] Follow-up visit 1 (FU1) = 30 days from the last dose +/- 7 days or coincide with the date of discontinuation (+/- 7 days) if date of discontinuation is greater than 37 days after last dose, Follow-up visit 2 (FU2) = 84 days (+/- 7 days) from follow-up visit 1

[b] Survival visits = every 3 months from FU2 +/- 7 days. BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window

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 interactive voice response system, including enrollment/randomization worksheets
- Manual for entry of local laboratory data
- Pregnancy Surveillance Forms
- RECIST 1.1 pocket guide

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 (see Section 5.1).

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, and Hep B and C testing (HBV sAg, HCV Ab or HCV RNA) (see Table 5.1-1). Pregnancy testing for WOCBP (done locally) must be performed within 24 hours prior to the initial administration of study drug at baseline and then within 24 hours of dosing at Week 1 and Week 4 of cycle 1 and 2, and Week 1 and Week 5 starting from cycle 3 and at the safety follow up visits.

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

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

On-study weight and ECOG Performance status should be assessed on Day 1 of Weeks 1, 3, 4 and 5 during cycles 1 and 2 (except Cycle 1 Day 1) and Day 1 of Weeks 1, 3 and 5 starting from Cycle 3 and vital signs should be assessed at each on-study visit (except Cycle 1 Day 1). 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 nivolumab blinded infusion 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 of dosing 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 on Day 1 of Weeks 1 and 4 for Cycles 1 and 2 and on Day 1 of Weeks 1 and 5 starting from Cycle 3. 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. 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 patient's 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 patient subject should be immediately evaluated to rule out pulmonary toxicity. An algorithm for the management of suspected pulmonary toxicity can be found in the nivolumab Investigator's 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 5.1. Baseline assessments should be performed within 28 days prior to randomization utilizing CT or MRI. In addition to chest, abdomen, pelvis, and brain, all known sites of disease should be assessed at baseline. Subsequent assessments should include chest, abdomen, and pelvis, and all known sites of disease and should use the same imaging method as was used at baseline. Subjects will be evaluated for tumor response beginning 12 weeks (± 1 week) from randomization and continuing every 6 weeks (± 1 week) for up to Week 49 from randomization and every 12 weeks (± 1 week)

thereafter, until disease progression is documented or treatment is discontinued (whichever occurs later). Tumor assessments for ongoing study treatment decisions will be completed by the investigator using RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 criteria. Radiographic images will be collected for independent radiological review committee tumor assessment.

5.4.1 Primary Efficacy Assessment

The co-primary endpoints of the study are progression free survival (PFS) and overall survival (OS) in all randomized subjects. See Section 8.3.1 for the definitions of PFS and OS.

5.4.2 Secondary Efficacy Assessment

The secondary efficacy endpoint of the study is ORR in all randomized subjects. See Section 8.3.2 for the definition of ORR.

5.4.3 Assessment of Overall Tumor Burden and Measurable Disease

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

At baseline, tumor lesions/lymph nodes will be categorized as measurable or nonmeasurable as follows in Sections 5.4.3.1, 5.4.3.2, and 5.4.3.3

5.4.3.1 Measurable Lesions

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

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

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

5.4.3.2 Non-Measurable Lesions

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

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

5.4.3.3 Special Considerations Regarding Lesion Measurability

Bone Lesions

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

Cystic Lesions

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

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

Non-measurable Lesions

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

5.4.4 Specifications by Method of Measurement

5.4.4.1 Measurement of Lesions

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

5.4.4.2 Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should

always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

5.4.4.3 CT/MRI Scan

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

5.4.4.4 Chest X-Ray

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

5.4.4.5 Clinical Lesions

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

5.4.4.6 Ultrasound

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

5.4.4.7 Endoscopy, Laparoscopy

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

5.4.4.8 Tumor Markers

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

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

5.4.5.1 Target Lesions

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

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

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

5.4.5.2 Lymph Nodes

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

5.4.5.3 Non-target Lesions

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

5.4.6 Tumor Response Evaluation

Evaluation of Target Lesions

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

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

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

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

5.4.6.1 Target Lesions that Become "Too Small to Measure"

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

5.4.6.2 Target Lesions that Split or Coalesce on Treatment

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

As lesions coalesce, a plane between them maybe maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

5.4.6.3 Evaluation of Non-target Lesions

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

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

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

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

5.4.6.4 Unequivocal Progression in Non-target Disease

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

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

5.4.7 New Lesions

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

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

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

5.4.8 Response Criteria (RECIST 1.1)

For subjects who have measurable disease at baseline, Table 5.4.8-1 provides a summary of the overall response status calculation at each time point.

Table 5.4.8-1: Time Point Response - Subjects With Target (± Non-target) Disease

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

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

5.4.8.1 Missing Assessments and Not Evaluable Designation

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

5.4.8.2 Confirmation of Scans

Verification of Response: Confirmation of response is not required since it will not add value to the interpretation of study results per RECIST 1.1.

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

5.4.9 Best Overall Response

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

For purposes of this study, the minimum scan time from baseline for determination of SD will be 9 weeks.

5.4.10 Duration of Objective Response

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

5.5 Pharmacokinetic Assessments

Pharmacokinetic blood samples will be drawn from study subjects assigned to all 3 treatment arms at the time points indicated in Table 5.5-1.

Table 5.5-1: Pharmacokinetic (PK) and Immunogenicity Sample Collections (CA209067)

Study Day[a]	Time (Relative To Dosing) Hour	Time (Relative To Dosing) Hour: Min	Pharmacokinetic Blood Sample for Nivolumab	Immunogenicity Blood Sample for Nivolumab	Pharmacokinetic Blood Sample for Ipilimumab	Immunogenicity Blood Sample for Ipilimumab
C1W1D1	0 (Predose)[b]	00:00	X	X	X	X
C1W1D1	1.0 (EOI-nivo)[c]	01:00	X			
C1W1D1	3.0 (EOI-ipi)[d]	03:00			X	
C1W3D1	0.0 (predose)[b]	00:00	X	X	X	X
C1W4D1	0.0 (predose)[b]	00:00	X	X	X	X
C2W1D1	0.0 (predose)[b]	00:00	X	X	X	X
C2W1D1	1.0 (EOI-nivo)[c]	01:00	X			
C2W1D1	3.0 (EOI-ipi)[d]	03:00			X	
C3W1D1	0.0 (predose)	00:00	X	X		
C4W1D1	0.0 (predose)[b]	00:00	X	X	X	X
C4W1D1	1.0 (EOI-nivo)	01:00	X	X		
First 2 Follow-up visits (approximately up to 100 days from the discontinuation of study drug	N/A	N/A	X	X		

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

[b] Predose: All pre-dose samples for nivolumab and ipilimumab should be taken prior to the start of nivolumab infusion.

[c] EOI-nivo: End of nivolumab Infusion. This sample should be taken immediately prior to stopping the nivolumab infusion (preferably within 2 minutes prior to end of infusion). If the end of nivolumab infusion is delayed, the collection of the infusion should be delayed accordingly.

[d] EOI-ipi: End of ipilimumab infusion. This sample should be taken immediately prior to stopping the ipilimumab infusion (preferably within 2 minutes prior to end of infusion.) 3 hour timepoint takes into account 30 min in between nivo and ipi dosing. If the end of ipilimumab infusion is delayed, the collection of this sample should be delayed accordingly.

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

5.6 Biomarker Assessments

A variety of factors that could potentially predict clinical response to nivolumab and/or nivolumab in combination with ipilimumab will be investigated in peripheral blood and in tumor specimens taken from all subjects prior to treatment and as outlined in Section 5.1. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. In addition, analyses of markers between the three treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value. All samples collected may also be used for future exploratory analyses (unless restricted by local requirements) to assess biomarkers associated with melanoma or immunotherapy treatment. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

5.6.1 Tumor Tissue Specimens

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

These tumor samples, as well as any solitary lesions that may have been surgically resected from subjects following an initial response (as described in section 3.4.3), or biopsy samples collected upon progression may also be assessed for the expression of other immune or melanoma related genes, RNAs and/or proteins, as well as, the presence of immune cell populations using a variety of methodologies inclusive of, but not limited to immunohistochemistry (IHC), qRT-PCR, genetic mutation detection and fluorescent in-situ hybridization (FISH). Various molecular markers with potential predictive value for the treatment of melanoma with nivolumab, ipilimumab and other immunotherapies are currently under investigation and may be assessed in this study. These tumor tissue biomarkers include, but are not limited to PD-1, PD-L2, tumor

infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature. In addition, other methods of measuring tumor PD-L1 expression may also be assessed. Tissue from the resected solitary lesions may be assessed for residual tumor cells and for markers expected to accompany tumor shrinkage in this study, including, but not limited to TILs and subsets therof.

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

5.6.2 Exploratory Serum Biomarkers

Blood samples for exploratory serum biomarker analyses will be drawn at the time points indicated in Section 5.1. Blood samples will be processed to collect serum and then put in frozen storage. Samples may be assessed by ELISA, seromics and/or other relevant multiplex-based protein assay methods for immune or melanoma-related factors that will predict for nivolumab or ipilimumab benefit or correlate with nivolumab or ipilimumab efficacy. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict or correlate with efficacy to nivolumab, ipilimumab or other immunotherapy, including but not limited to levels of soluble PD-L1, anti-tumor antibodies, cytokines, chemokines, inflammatory factors and microRNAs (such as, but not limited to, miR-513 and miR19b).

5.6.3 Peripheral Blood Mononuclear Cells (PBMCs)

Peripheral blood samples will be taken prior to initiation of study therapy and at designated timepoints on-treatment (see Section 5.1 for additional details on the blood sample collection schedule) for PBMC preparation. Samples must be shipped within 48 hours to a BMS-designated central laboratory for processing.

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

5.6.4 Peripheral Blood RNA

While immunophenotyping of peripheral blood will provide valuable information on the modulation of the composition of immune cells in the periphery, gene expression analyses of RNA derived from whole blood may provide information on the broad effects of nivolumab and ipilimumab on immune modulation. Thus, genomic expression patterns of whole blood collected at baseline and during on-study treatment as specified in Table 5.1-2 may be assessed by

Affymetrix microarray profiling, qRT-PCR or other gene expression profiling technology, with a particular emphasis on genes with relevant immune function. In addition, RNA or DNA derived from this peripheral blood sample may be assessed for rearrangements in the T cell receptor (TCR) in T cells within the peripheral blood. An assessment of somatic TCR rearrangements by PCR, sequencing or NextGen sequencing approach will provide information regarding the clonality of a T cell repertoire, which may change with nivolumab and/or ipilimumab treatment. In addition, baseline T cell repertoire may be predictive of nivolumab and/or ipilimumab benefit.

5.6.5 Whole Blood for SNP Assessment

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

5.7 Outcomes Research Assessments

HRQoL will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is the most commonly used QoL instrument in advanced melanoma clinical studies.

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

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

Work Productivity and Activity Impairment: General Health (WPAI:GH).

This questionnaire is a 6-item questionnaire yielding four different types of scores. The WPAI:GH was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work /reduced on-the-job effectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The recall period in all WPAI validation studies is 7 days. The

general literature on recall burden suggests that a longer recall period would not be suitable for the type of information being elicited in the WPAI. In theory, a shorter recall period would improve accuracy of WPAI responses, but this has not been tested. Assessment of work productivity will be conducted at each site (or remotely) with the appropriately translated and validated version of the WPAI.

The quality of survival in patients after treatment discontinuation will be characterized by measuring the health related quality of life (HRQoL), using the EQ-5D with VAS as outlined in Table 5.1-4.

All PRO instruments will be administered during on-study, and follow-up phases as outlined in Section 5.1, 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 Table 5.1-2, Table 5.1-3, and Table 5.1-4.

5.8 Other Assessments

5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analyses of nivolumab and/or ipilimumab will be collected according to the schedule given in Table 5.5-1. Samples collected from subjects in each treatment arm will be evaluated for development of Anti-Drug Antibody (ADA) for nivolumab and/or ipilimumab by validated immunoassays. Samples may also be analyzed for neutralizing ADA response to nivolumab and/or ipilimumab. (Neutralizing ADA testing conditioned upon assay availability.)

5.9 Results of Central Assessments

Not applicable.

6 ADVERSE EVENTS

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

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

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events

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

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

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

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

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

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

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

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

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

SAE Email Address: See Contact Information list.

SAE Facsimile Number: See Contact Information list.

For studies capturing SAEs through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only

in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

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

All SAEs should be followed to resolution or stabilization.

6.2 Nonserious Adverse Events

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

6.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at initiation of study drug. Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

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

All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

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

6.3 Laboratory Test Result Abnormalities

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

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

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

6.4 Pregnancy

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

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

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

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

Potential drug induced liver injury is defined as:

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

   AND

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

   AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee will be established to provide oversight and safety and efficacy considerations in protocol CA209067 and to 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. 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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

Approximately 915 subjects will be randomized to three treatment arms in a 1:1:1 ratio. The sample size of the study accounts for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS), with an alpha allocation of 0.01 for PFS and 0.04 for OS.

Formal analyses of PFS and OS will be conducted at different timepoints.

- The PFS analysis is targeted to occur after all subjects have 9 months follow-up per sample size and power considerations (Section 8.1.1). However, the required minimum follow-up for analysis of PFS is 6 months.
- The OS analysis is targeted to occur after all subjects have 28 months follow-up per sample size and power considerations (Section 8.1.2). However, the required minimum follow-up for analysis of OS is 22 months.

In time-to-events trials, the number of events and power may typically be calculated assuming an exponential distribution in each treatment arm. However for PFS, a delayed separation in curves may be observed in this study as a result of the first tumor assessment being scheduled for Week 12. In addition, a meaningful number of long term survivors have been reported in clinical studies that evaluated immuno-oncologic therapy and such a phenomenon was present in the pivotal first-line ipilimumab Phase 3 studies MDX010-20 and CA184024. As a consequence, the survival curves in this study may not follow an exponential decay and a flattening of the curves may be observed toward the end of this study. Therefore to provide more accurate calculations, the number of events and power are calculated using statistical models based on PFS and OS data external to this study, as noted below. Details of the modeling are presented in the SAP.

A piecewise constant accrual rate (30 subjects during Months 1 and 2, 75 subjects during Month 3, 120 subjects during Month 4, 150 subjects during Month 5, 375 subjects during Month 6, 45 subjects during Month 7, and 90 subjects during Month 8) is assumed. Approximately 8 months is required to enroll the required number of subjects.

8.1.1 Progression Free Survival

For each PFS comparison, the number of events projected to be observed at 9 months follow-up provide approximately 83% power to detect an average hazard ratio (HR) of 0.71 with a Type I error of 0.005 (two-sided). This modeling assumes PFS medians of 2.8 and 3.1 months, 6 month PFS rates of 21.6% and 36.9%, and 12 month PFS rates of 12.8% and 26.9% in the control arm and experimental arms, respectively. Assuming the distribution of events follows the alternative hypothesis, approximately 266 PFS events in the control group and 223 PFS events in each of the experimental groups are expected at the time of analysis. Calculations are based on statistical models using PFS data from study MDX010-20 for the control arm and PFS data from study CA209038 for the experimental arms. A Bonferroni adjustment will be applied to control the overall Type I error rate at 0.01 for PFS.

8.1.2 Overall Survival

For each OS comparison, the number of events projected to be observed at 28 months of follow-up provide approximately 99% power to detect an average HR of 0.65 with a Type I error of 0.02 (two-sided). This modeling assumes OS medians of 10.2 and 17.2 months, 12 month OS rates of 43.9% and 62.1%, and 24 month OS rates of 24.4% and 39.6% in the control arm and experimental arms, respectively. Assuming the distribution of events follows the alternative hypothesis, approximately 240 OS events in the control group and 202 OS events in each of the experimental groups are expected at the time of analysis. Calculations are based on statistical models using OS data from study MDX010-20 for the control arm and OS data from study CA209003 for the experimental arms. Hochberg's procedure[62] will be applied to control the overall Type I error rate at 0.04 for OS.

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 group.
- All Treated Subjects: All subjects who received at least one dose of any study medication.
- PK Subjects: All randomized subjects with available serum time-concentration data.
- Immunogenicity Subjects: All randomized subjects with available ADA data.
- Biomarker Subjects: All randomized subjects with available biomarker data.

8.3 Endpoints

8.3.1 Co-Primary Endpoint(s)

The primary objective will be measured by the co-primary endpoints of PFS and OS in all randomized subjects.

8.3.1.1 Progression Free Survival

PFS is defined as the time between the date of randomization and the first date of documented progression, as determined by the investigator, or death due to any cause, whichever occurs first. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on their date of randomization. Subjects who started anti-cancer therapy without a prior reported progression will be censored on the date of their last evaluable tumor assessment prior to the initiation of subsequent anti-cancer therapy. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 Weeks until disease progression.

8.3.1.2 Overall Survival

OS is defined as the time between the date of randomization and the date of death due to any cause. OS will be censored on the last date a subject was known to be alive. OS data will be collected continuously while subjects are on study medication and every 3 months via in-person or phone contact after discontinuation of study medication.

8.3.2 Secondary Endpoint(s)

The first secondary objective (to compare ORR between the experimental arms and the control group) will be measured by the endpoint of ORR. The ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of objectively documented progression per RECIST 1.1 or the date of subsequent anti-cancer therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment. Tumor assessments are scheduled to be performed at Week 12, every 6 Weeks up to Week 49 and then every 12 Weeks until disease progression.

The second secondary objective (to evaluate differences in OS, PFS, and ORR between the two experimental arms) and will be measured by the endpoints of OS, PFS, and ORR.

The third secondary objective (to evaluate PD-L1 expression as a predictive biomarker) will be measured by the endpoints of PFS and OS based on PD-L1 expression level. PD-L1 expression will be evaluated in tumor specimens collected prior to randomization.

The fourth secondary objective (to evaluate HRQoL) will be measured by mean changes from baseline in the EORTC-QLQ-C30 global health status/QoL composite scale and by mean changes from baseline in the remaining EORTC QLQ-C30 scales. HRQoL will be evaluated per Section 5.1

8.3.3 Exploratory Endpoint(s)

Duration of and time to response will be measured by the endpoints duration of objective response (DOOR) and time to objective response (TTOR). DOOR is defined as the time between the date of first response to the date of first documented tumor progression (per RECIST 1.1) or death due to any cause. Subjects who neither progress nor die will be censored on the date of their last tumor assessment. TTOR is defined as the time from randomization to the date of the first documented CR or PR. DOOR and TTOR will be evaluated for responders (CR or PR) only.

Safety and tolerability will be measured by the incidence of adverse events, serious adverse events, deaths, and laboratory abnormalities.

Pharmacokinetics will be measured using serum concentration-time data.

Other exploratory endpoints for biomarkers, pharmacogenomics, and immunogenicity are described in Sections 5.6 and 5.8.

8.4 Analyses

Formal analyses of PFS and OS will be conducted at different time points with PFS being analyzed first (PFS analysis timepoint) followed by analysis of OS (OS analysis timepoint). Except where otherwise noted, analyses will be conducted at both timepoints.

8.4.1 Demographics and Baseline Characteristics

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

8.4.2 Efficacy Analyses

8.4.2.1 Primary Endpoint Methods

Primary Endpoint Methods at PFS Analysis Timepoint

Each of the two primary PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening in randomized subjects to compare each of the two experimental treatments to the control group. Hazard ratios (HR) and corresponding two-sided 99.5% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology.

Additionally, OS curves, OS medians with 95% CIs, and OS rates at 12 months with 95% CIs will be estimated using Kaplan-Meier methodology. HRs and corresponding

two-sided 99.99% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. There will be no formal comparison of OS at the PFS analysis timepoint.

Primary Endpoint Methods at OS Analysis Timepoint

Each of the two primary OS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening in all randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided 98% CIs will be estimated using a Cox proportional hazards model, with treatment group 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.

Additionally, PFS curves, PFS medians with 95% CIs, and PFS rates at 6 and 12 months with 95% CIs will be estimated using Kaplan-Meier methodology. HRs and corresponding two-sided 99.99% CI will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. There will be no formal comparison of PFS at the OS analysis timepoint.

8.4.2.2 Secondary Endpoint Methods

Secondary Endpoint Methods at PFS Analysis Timepoint

If PFS superiority is demonstrated for either experimental versus control comparison, a gatekeeping testing approach for ORR will be applied as described in the statistical analysis plan. The alpha level retained for testing of ORR will depend on whether one or both PFS comparisons are positive and ensure that the overall type I error is adequately maintained.

ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage at screening to compare each of the two experimental treatments to the control group. Associated odds ratios and (1-adjusted α)% CIs will be calculated. Additionally, ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental arms, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

The totality of PFS results will be summarized in a single graphical display that includes Kaplan-Meier curves for the three treatment arms, the log-rank p-values for the two formal comparisons, the three HRs and corresponding CIs, and the three KM medians and corresponding CIs.

To assess the potential association between PD-L1 expression and PFS, PFS curves and medians with 95% CIs will be estimated using Kaplan-Meier methodology by treatment group for each PD-L1 expression categories and for subjects with a missing or indeterminate PD-L1 IHC result.

Potential associations with ORR will also be examined. If there is an indication of a meaningful association, additional analyses may be performed to further evaluate PD-L1 expression as a predictive biomarker.

Secondary Endpoint Methods at OS Analysis Timepoint

ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms. Odds ratios and 95% CIs will be calculated.

Descriptive analyses of OS, PFS, and ORR will be performed to evaluate differences between the two experimental arms, nivolumab combined with ipilimumab and nivolumab monotherapy. These include HRs and medians with corresponding two-sided 95% CIs for OS and PFS, as well as an ORR odds ratio with corresponding 95% CI.

The totality of OS results will be summarized in a single graphical display that includes Kaplan-Meier curves for the three treatment arms, the log-rank p-values for the two formal comparisons, the three HRs and corresponding CIs, and the three KM medians and corresponding CIs. PFS results will be summarized similarly.

To assess the potential association between PD-L1 expression and OS, OS curves and medians with 95% CIs will be estimated using Kaplan-Meier methodology by treatment group for each PD-L1 expression categories and for subjects with a missing or indeterminate PD-L1 IHC result. If there is an indication of a meaningful association, additional analyses may be performed to further evaluate PD-L1 expression as a predictive biomarker.

8.4.3 Safety Analyses

Safety analyses will be performed in all treated subjects. Descriptive statistics of safety will be presented using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment group. All on-study AEs, 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.

8.4.4 Pharmacokinetic Analyses

The concentration vs time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug- drug interaction between nivolumab and ipilimumab will be studied by population PK approach. Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately.

8.4.5 Biomarker Analyses

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

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 group. Exploratory analyses may be performed to examine differences between the two groups.

8.4.7 Other Analyses

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

Radiographic images will be collected for independent radiological review committee tumor assessment. Details for the analyses are described in the independent radiologic review committee charter.

8.5 Interim Analyses

Not applicable.

9 STUDY MANAGEMENT

9.1 Compliance

9.1.1 Compliance with the Protocol and Protocol Revisions

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

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

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

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

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

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

9.1.2 Monitoring

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

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

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

9.1.3 Investigational Site Training

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

9.2 Records

9.2.1 Records Retention

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

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

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

9.2.2 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by BMS) is maintained at each study site where study drug are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

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

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

9.2.3 Case Report Forms

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

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

The confidentiality of records that could identify subjects must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF, including any paper or electronic SAE/pregnancy CRFs, must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a subinvestigator and who is delegated this task on the Delegation of Authority Form .For electronic CRFs, review and approval/signature is completed electronically through the BMS electronic data capture tool. The investigator must retain a copy of the CRFs including records of the changes and corrections.

Each individual electronically signing electronic CRFs must meet BMS training requirements and must only access the BMS electronic data capture tool using the unique user account provided by BMS. User accounts are not to be shared or reassigned to other individuals.

9.3 Clinical Study Report and Publications

A Signatory Investigator must be selected to sign the clinical study report.

For this protocol, the Signatory Investigator will be selected considering the following criteria:

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

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

10 GLOSSARY OF TERMS

Term	Definition
Adverse Reaction	An adverse event that is considered by either the investigator or BMS as related to the investigational product
Unexpected Adverse Reaction	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, Investigator Brochure for an unapproved investigational product)
Serious Adverse Event	Serious adverse event defined as any untoward medical occurrence that at any dose: results in death; is life threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe), requires inpatient hospitalization or causes prolongation of existing hospitalization; results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect; is an important medical event (defined as a medical event(s) that may not be immediately life threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.). For reporting purposes only, BMS also considers the occurrence of pregnancy, overdose (regardless of association with an AE), and cancer as important medical events.

11 LIST OF ABBREVIATIONS

Term	Definition
AE	adverse event
ACLS	advanced cardiac life support
ADL	Activities of daily living
AI	accumulation index
AI_AUC	AUC Accumulation Index; ratio of AUC(TAU) at steady state to AUC(TAU) after the first dose
AI_Cmax	Cmax Accumulation Index; ratio of Cmax at steady state to Cmax after the first dose
AI_Ctau	Ctau Accumulation Index; ratio of Ctau at steady state to Ctau after the first dose
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANOVA	analysis of variance
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AT	aminotransaminases
AUC	area under the concentration-time curve
AUC(INF)	area under the concentration-time curve from time zero extrapolated to infinite time
AUC(0-T)	area under the concentration-time curve from time zero to the time of the last quantifiable concentration
AUC(TAU)	area under the concentration-time curve in one dosing interval
A-V	atrioventricular
β-HCG	beta-human chorionic gonadotrophin
BA/BE	bioavailability/bioequivalence
%BE	percent biliary excretion
BID, bid	bis in die, twice daily
BLQ	below limit of quantification
BMI	body mass index
BMS	Bristol-Myers Squibb

Term	Definition
BP	blood pressure
BRt	Total amount recovered in bile
%BRt	Total percent of administered dose recovered in bile
BSA	Body surface area
BUN	blood urea nitrogen
C	Celsius
C12	concentration at 12 hours
C24	concentration at 24 hours
Ca^{++}	calcium
Cavg	average concentration
CBC	complete blood count
Cexpected-tau	expected concentration in a dosing interval
CFR	Code of Federal Regulations
CI	confidence interval
$C1^{-}$	chloride
CLcr	creatinine clearance
CLD	Dialysate clearance of drug from plasma/serum
CLNR	nonrenal clearance
CLR	renal clearance
CLT	total body clearance
CLT/F (or CLT)	apparent total body clearance
CLT/F/fu or CLT/fu	Apparent total body clearance of free drug or Total body clearance of free drug (if IV)
cm	centimeter
Cmax, CMAX	maximum observed concentration
Cmin, CMIN	trough observed concentration
CNS	Central nervous system
CRC	Clinical Research Center
CRF	Case Report Form, paper or electronic
Ct	Expected concentration at a certain time, usually at the end of an expected future dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)

Term	Definition
Ctau	Concentration in a dosing interval (eg, concentration at 24 hours, concentration at 12 hours, etc.)
Ctrough	Trough observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
CYP	cytochrome p-450
D/C	discontinue
dL	deciliter
DRt	Total amount recovered in dialysate
%DRt	Total percent of administered dose recovered in dialysate
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} Edition)
EA	extent of absorption
ECG	electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EEG	electroencephalogram
eg	exempli gratia (for example)
ESR	Expedited Safety Report
F	bioavailability
Fb	fraction of bound drug
FDA	Food and Drug Administration
FI	fluctuation Index ([Cmax-Ctau)/Cavg])
FRt	total amount recovered in feces
%FRt	total percent of administered dose recovered in feces
FSH	follicle stimulating hormone
fT4	Free thyroxine
%FE	percent fecal excretion
fu	fraction of unbound drug
g	gram
G	Grade
GC	gas chromatography
GCP	Good Clinical Practice

Term	Definition
G criteria	adjusted R^2 value of terminal elimination phase
GGT	gamma-glutamyl transferase
GFR	glomerular filtration rate
h(hrs)	Hour (hours)
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCO_3^-	bicarbonate
HIV	Human Immunodeficiency Virus
HR	heart rate
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICH	International Conference on Harmonisation
ID	Infectious Disease
ie	id est (that is)
IEC	Independent Ethics Committee
IMP	investigational medicinal products
IND	Investigational New Drug Exemption
I/O	Immuno-oncology
IRB	Institutional Review Board
IU	International Unit
IV	intravenous
IVIG	Intravenous immunoglobulin
K	slope of the terminal phase of the log concentration-time curve
K_3EDTA	potassium ethylenediaminetetraacetic acid
K^+	potassium
kg	kilogram
λz	terminal disposition rate constant
L	liter
LC	liquid chromatography

Term	Definition
LDH	lactate dehydrogenase
ln	natural logarithm
LFT	Liver function test
Lz_Start	The time point starting the log-linear elimination phase defining ther terminal half life
Lz_End	The time point ending the log-linear elimination phase defining the terminal half life
Lz_N	Number of time points in the log-linear elimination phase defining the terminal half life
mg	milligram
Mg/kg	Milligram per kilogram
Mg^{++}	magnesium
MIC	minimum inhibitory concentration
min	minute
mL	milliliter
mmHg	millimeters of mercury
MR_AUC(0-T)	Ratio of metabolite AUC(0-T) to parent AUC(0-T), corrected for molecular weight
MR_AUC(INF)	Ratio of metabolite AUC(INF) to parent AUC(INF), corrected for molecular weight
MR_AUC(TAU)	Ratio of metabolite AUC(TAU) to parent AUC(TAU), corrected for molecular weight
MR_Cmax	Ratio of metabolite Cmax to parent Cmax, corrected for molecular weight
MR_Ctau	Ratio of metabolite Ctau to parent Ctau, corrected for molecular weight
MRI	Magnetic resonance imaging
MRT	mean residence time
MS	mass spectrometry
MTD	maximum tolerated dose
μg	microgram
N	number of subjects or observations
Na^{+}	sodium
N/A	not applicable

Term	Definition
NCI	National Cancer Institute
ng	nanogram
NIMP	non-investigational medicinal products
NSAID	nonsteroidal anti-inflammatory drug
pAUCe	Extrapolated partial AUC from last quantifiable concentration to infinity
ORR	Objective Response Rate
OS	Overall Survival
Pb	percent of bound drug
PD	pharmacodynamics
PFS	Progression Free Survival
PK	pharmacokinetics
PO	per os (by mouth route of administration)
PT	prothrombin time
PTT	partial thromboplastin time
Pu	percent of unbound drug
QC	quality control
QD, qd	quaque die, once daily
R^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
SD	standard deviation
SOP	Standard Operating Procedures
sp.	species
Subj	subject
t	temperature
T	time
TAO	Trial Access Online, the BMS implementation of an EDC capability
T.bili	Total bilirubin
T-HALF	Half life
T-HALFeff_AUC	Effective elimination half life that explains the degree of AUC accumulation observed

Term	Definition
T-HALFeff_Cmax	Effective elimination half life that explains the degree of Cmax accumulation observed)
TID, tid	ter in die, three times a day
Tmax, TMAX	time of maximum observed concentration
TR_AUC(0-T)	AUC(0-T) treatment ratio
TR_AUC(INF)	AUC(INF) treatment ratio
TR_Cmax	Cmax treatment ratio
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UR	urinary recovery
%UR	percent urinary recovery
URt	total amount recovered in urine
%URt	total percent of administered dose recovered in urine
UV	ultraviolet
Vss/F (or Vss)	apparent volume of distribution at steady state
Vz	Volume of distribution of terminal phase (if IV and if multi-exponential decline)
W	washout
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential
x g	times gravity

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APPENDIX 1 ADDITIONAL ETHICAL CONSIDERATIONS

1 INFORMED CONSENT PROCEDURES

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.

The consent form must also include a statement that BMS and regulatory authorities have direct access to subject records. Prior to the beginning of the study, the investigator must have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects.

The investigator must provide the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative with a copy of the consent form and written information about the study in the language in which the subject is most proficient. The language must be non-technical and easily understood. The investigator should allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study, then informed consent must be signed and personally dated by the subject or the subject's legally acceptable representative and by the person who conducted the informed consent discussion. The subject or legally acceptable representative should receive a copy of the signed informed consent and any other written information provided to study subjects prior to subject's participation in the study.

1.1 Subjects Unable to Give Written Informed Consent

1.1.1 Minors

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. (In the event that the parents or legal guardians are unable to read, then an impartial witness should be present during the entire informed consent discussion). Whenever feasible, minors who are judged to be of an age of reason must also give their written assent by signing and dating the completed informed consent. All local laws, rules and regulations regarding informed consent of minors must be followed.

1.1.2 Subjects Experiencing Acute Events or Emergencies

A legally acceptable representative or legal guardian must provide informed consent when consent of the subject is not possible prior to clinical study participation, eg, for subjects experiencing an acute medical event such as myocardial infarction or stroke. Informed consent of the subject must additionally be obtained if they become capable of making and communicating their informed consent during the clinical study. All local laws, rules and regulations regarding informed consent of adult subjects incapable of giving informed consent must be followed.

1.1.3 Mentally Impaired or Incapacitated Subjects

Investigators (or whoever required by local regulations) should determine whether or not a mentally impaired or incapacitated subject is capable of giving informed consent and should sign a statement to that effect. If the subject is deemed mentally competent to give informed consent, the investigator should follow standard procedures. If the subject is deemed not to be mentally competent to give informed consent, a fully informed legal guardian or legally acceptable representative can be asked to give consent for, or on behalf of, the subject. All local laws, rules and regulations regarding informed consent of mentally impaired or incapacitated subjects must be followed.

Patients who are involuntarily hospitalized because of mental illness must not be enrolled in clinical studies

1.1.4 Other Circumstances

Subjects who are imprisoned or involuntarily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness must not be enrolled in clinical studies.

In circumstances where a subject's only access to treatment is through enrollment in a clinical study, eg, for subjects in developing countries with limited resources or for subjects with no marketed treatment options, the investigator must take special care to explain the potential risks and benefits associated with the study and ensure that the subject is giving informed consent.

When a subject may be in a dependent relationship with the investigator, a well-informed physician who is not engaged in the clinical study and is completely independent of the relationship between the subject and investigator should obtain the subject's informed consent.

1.1.5 Illiterate Subjects

If the subject, or, in those situations where consent cannot be given by the subject, their legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's rights to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject, or, in those situations where consent cannot be given by subjects, their legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

1.2 Update of Informed Consent

The informed consent and any other information provided to subjects, or, in those situations where consent cannot be given by subjects, the subject's legally acceptable representative, should be revised whenever important new information becomes available that is relevant to the subject's consent, and should receive IRB/IEC approval/favorable opinion prior to use. The investigator, or a person designated by the investigator should fully inform the subject or the

subject's legally acceptable representative 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.

During a subject's participation in the study, any updates to the consent form and any updates to the written information will be provided to the subject.

APPENDIX 2 PERFORMANCE STATUS SCALES

STATUS	SCALES		STATUS
	KARNOFSKY	**ZUBROD-ECOG-WHO**	
Normal, no complaints	100	0	Normal activity
Able to carry on normal activities Minor signs or symptoms of disease	90	0	Symptoms, but fully ambulatory
Normal activity with effort	80	1	
Cares for self. Unable to carry on normal activity or to do active work	70	1	Symptomatic, but in bed < 50% of the day.
Requires occasional assistance, but able to care for most of his needs	60	2	
Requires considerable assistance and frequent medical care	50	2	Needs to be in bed > 50% of the day, but not bedridden
Disabled. Requires special care and assistance	40	3	
Severely disabled. Hospitalization indicated though death non imminent	30	3	
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Unable to get out of bed
Moribund	10	4	
Dead	0	5	Dead

APPENDIX 3 M STAGE CATEGORIES FOR CUTANEOUS MELANOMA

M Stage Categories for Cutaneous Melanoma[a]		
M	**Site**	**Serum LDH[b]**
M0	No distant metastases	Not applicable
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

[a] Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 2009; 27:6199-6206.

[b] LDH - Lactate dehydrogenase

APPENDIX 4 MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy

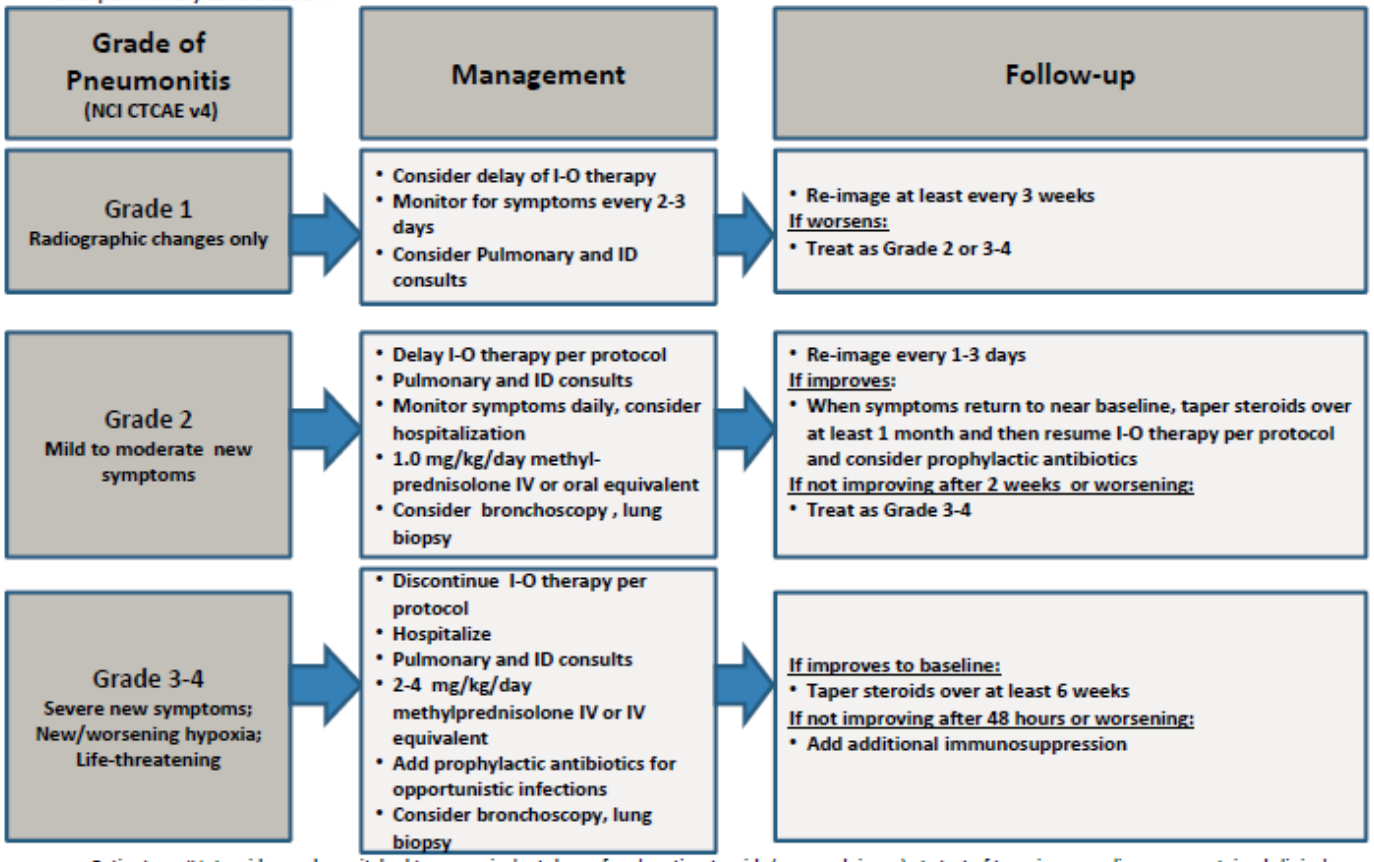
Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	If returns to baseline: •Resume routine creatinine monitoring per protocol If worsens: •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	If returns to Grade 1: •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol If elevations persist > 7 days or worsen: •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	If returns to Grade 1 : Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

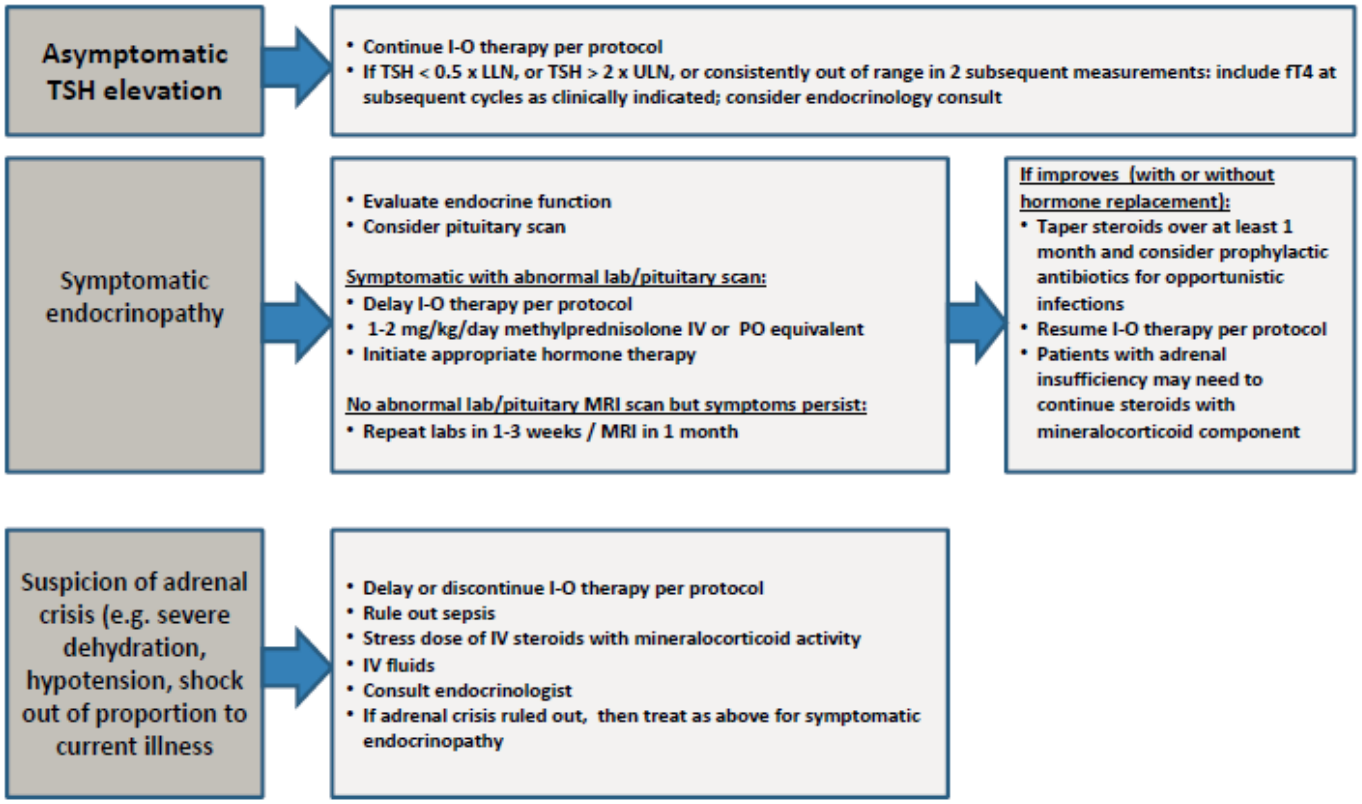
Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.
**The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

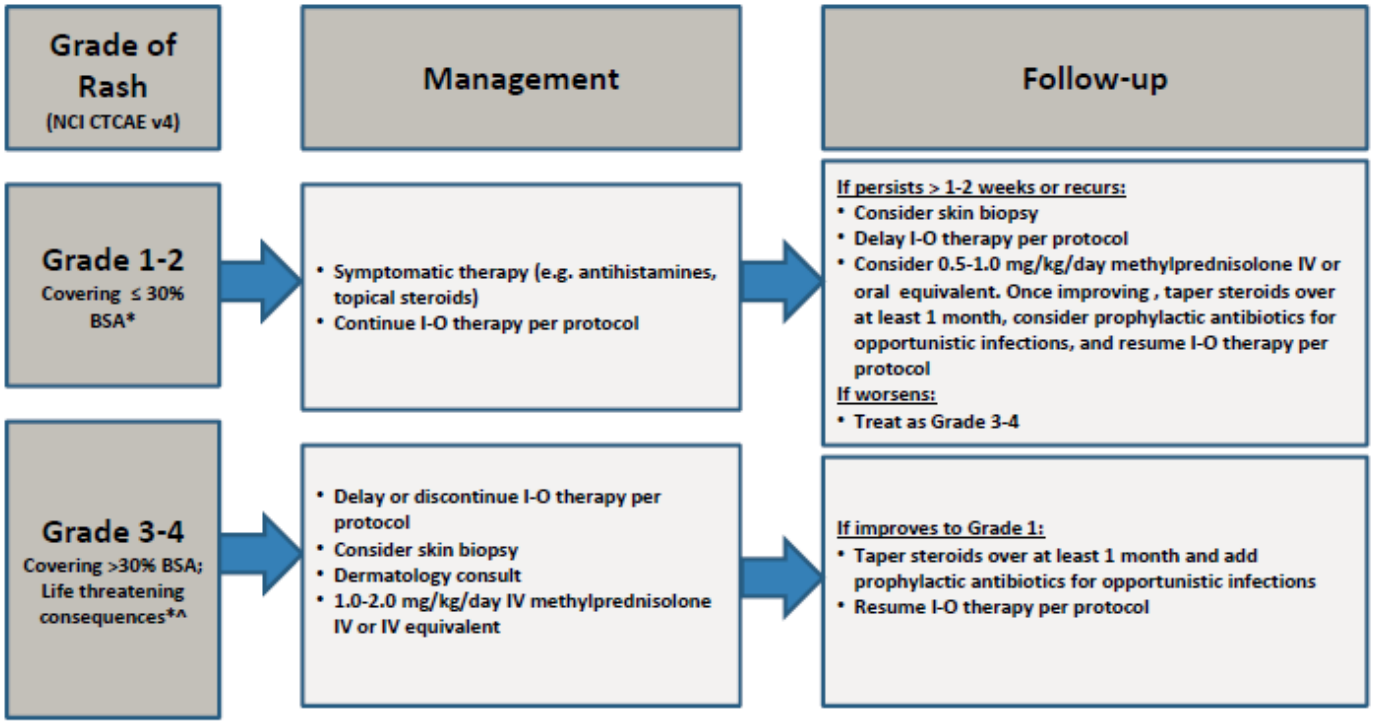


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Updated 05-Jul-2016

Neurological Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Updated 05-Jul-2016

APPENDIX 5 WOMEN OF CHILDBEARING POTENTIAL: METHODS OF CONTRACEPTION

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILD BEARING POTENTIAL

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

Local laws and regulations may require use of alternative and/or additional contraception methods.

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of <1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] – oral – intravaginal – transdermal
• Progestogen-only hormonal contraception associated with inhibition of ovulation[b] – oral – injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation [b] • Hormonal methods of contraception including oral contraceptive pills containing a combination of estrogen and progesterone, vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

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

NOTES:

[a] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized.

[c] Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness

Unacceptable Methods of Contraception

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

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

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

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

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

DOCUMENT HISTORY

Document	Date of Issue	Summary of Change
Revised Protocol 06	20-Oct-2017	Incorporates Amendment 11 and Administrative Letters 02, 03, 04 and 05.
Amendment 11	20-Oct-2017	Prior to implementation of this amendment, following completion of the primary efficacy analysis, maintenance of the blind was no longer required for study purposes and all subjects were unblinded. The purpose of this amendment is to provide instructions for unblinded subjects remaining on study treatment or in follow-up.
Administrative Letter 05	26-Jul-2017	Change in Medical Monitor
Administrative Letter 04	17-Jul-2017	Change in Medical Monitor
Administrative Letter 03	10-Jul-2017	Change in Medical Monitor
Administrative Letter 02	02-Feb-2017	Update to Medical Monitor Address
Revised Protocol 05	12-Oct-2016	Incorporates Amendment 10
Amendment 10	12-Oct-2016	The main purpose of this protocol amendment is necessary following a recent update to the Nivolumab Investigator's Brochure version 15, Erratum 01, including those related to the use of contraceptives, and updated Appendix 5. Additionally, updated Tumor Assessment scan frequency in the Follow-up and Survival phase.
Revised Protocol 04	19-May-2015	Incorporates Administrative letter 01 and Amendment 08
Amendment 08	19-May-2015	The purpose of this amendment is to allow for future collection of survival status outside of the protocol-defined windows if necessary, correct errors and update Appendix 5 Methods of Contraception as well as SAE reporting language.
Administrative letter 01	24-Feb-2015	Change in Study Director/Medical Monitor
Revised Protocol 03	16-Jan-2015	Incorporates Amendment 07
Amendment 07	16-Jan-2015	The main purpose of Amendment 07 is to add the collection of radiographic images for review by an independent radiological review committee. No other changes are included in this amendment.
Revised Protocol 02	27-Jun-2014	Incorporates Amendment 06
Amendment 06	27-Jun-2014	The main purpose of Amendment 06 is to change the secondary objective to add PFS as a co-primary objective. • Additional modification are as described below: • Revise Research Hypothesis, Study Rationale, Primary Endpoints to include PFS as a co-primary objective/endpoint. • Add rationale for inclusion of PFS as a co-primary endpoint. • Revise statistical section 8 to include analyses related to PFS.

Document	Date of Issue	Summary of Change
Revised Protocol 01	20-Aug-2013	Incorporates Amendment 04
Amendment 04	20-Aug-2013	The main purpose of the first global amendment is to add a recommendation to perform an optional tumor biopsy when assessing whether to treat beyond progression per a Health Authority request. This biopsy can be used to assess the impact of treatment on relevant melanoma biomarkers including BRAF mutation status and investigate potential mechanisms of resistance to immunotherapeutic agents. Additional modifications are as described below: • Allow palliative radiotherapy and palliative surgery if the following criteria are met: ◦ The subject is considered to have progressed at the time of palliative therapy and meets criteria to continue with treatment beyond progression. ◦ The case is discussed with the BMS medical monitor. Palliative therapy must be clearly documented as such in the study record. • Asymptomatic elevations in amylase and lipase not associated with symptoms or clinical manifestations of pancreatitis were removed from the dose delay or discontinuation criteria. It is considered acceptable for the following reasons: ◦ Asymptomatic elevations of amylase or lipase have not been proven to have independent clinical consequence or predict for development or severity of pancreatitis ◦ A wide variation of asymptomatic elevations in amylase or lipase can occur on a day-to-day basis, limiting the utility of interpreting the amylase or lipase elevations in isolation. • Updated the Adverse Event Management Algorithms to be consistent with the Nivolumab IB v.12 • Add background information on opportunistic infections and recommendations for prophylactic antibiotics in the setting of greater than 4 weeks of corticosteroid or immunosuppressant administration • Clarify that either HCV antibody or HCV RNA testing is allowed to determine HCV status • Clarify exclusion criteria to exclude only subjects that participated in a blinded Phase 3 ipilimumab study • Incorporate other minor changes to correct and/or clarify protocol requirements
Amendment 01	19-Mar-2013	PGx
Original Protocol	19-Mar-2013	Not applicable

STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINED WITH IPILIMUMAB VERSUS IPILIMUMAB MONOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED UNRESECTABLE OR METASTATIC MELANOMA

PROTOCOL(S) CA209067

VERSION # 1.0

Approved v2.0 930075901 1.0

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1 BACKGROUND AND RATIONALE

CA209067 (CheckMate 067, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. Ipilimumab was chosen as the comparator because it is FDA and EMA approved in subjects with unresectable or metastatic melanoma and currently utilized for previously untreated melanoma patients in the US. It is the only FDA or EMA approved therapy for unresectable or metastatic melanoma that has demonstrated overall survival benefit in a randomized Phase 3 trial that is not BRAF mutational status restricted. Nivolumab monotherapy was chosen as one of the experimental arms because of a favorable risk-benefit ratio assessed in the large Phase 1 study (MDX1106-03/CA209003). The combination of nivolumab and ipilimumab was chosen as an experimental arm because of the preliminary evidence from the Phase 1 study CA209004 suggesting synergy between nivolumab and ipilimumab resulting in a higher frequency of patients with increased magnitude of tumor burden reduction. Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on their individual risk-benefit ratio.

This document contains descriptions of the statistical analyses that will be conducted for the Clinical Study Report (CSR) of study CA209-067. This document also refers to Core Safety Statistical Analysis Plan[1] that contains program level safety analyses descriptions.

Research Hypothesis:

Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve overall survival when compared to ipilimumab monotherapy in previously untreated subjects with unresectable or metastatic melanoma.

Schedule of Analyses:

OS is the primary endpoint for this study; OS will be compared 1) between nivolumab and ipilimumab and 2) between nivolumab combined with ipilimumab and ipilimumab.

The final analysis of the two OS comparisons will occur when approximately 247 events (ie deaths) in the control group have been observed. All other endpoints will be analyzed at the time of this final OS analysis. No interim analysis will be performed.

An independent Data Monitoring Committee (DMC) will monitor the study and have access to periodic interim safety and efficacy reports to allow for a risk/benefit assessment. Details are specified in the DMC Charter[2].

2 STUDY DESCRIPTION

2.1 Study Design

This is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with

previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable Stage III or stage IV melanoma, as per the AJCC staging system, and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization.

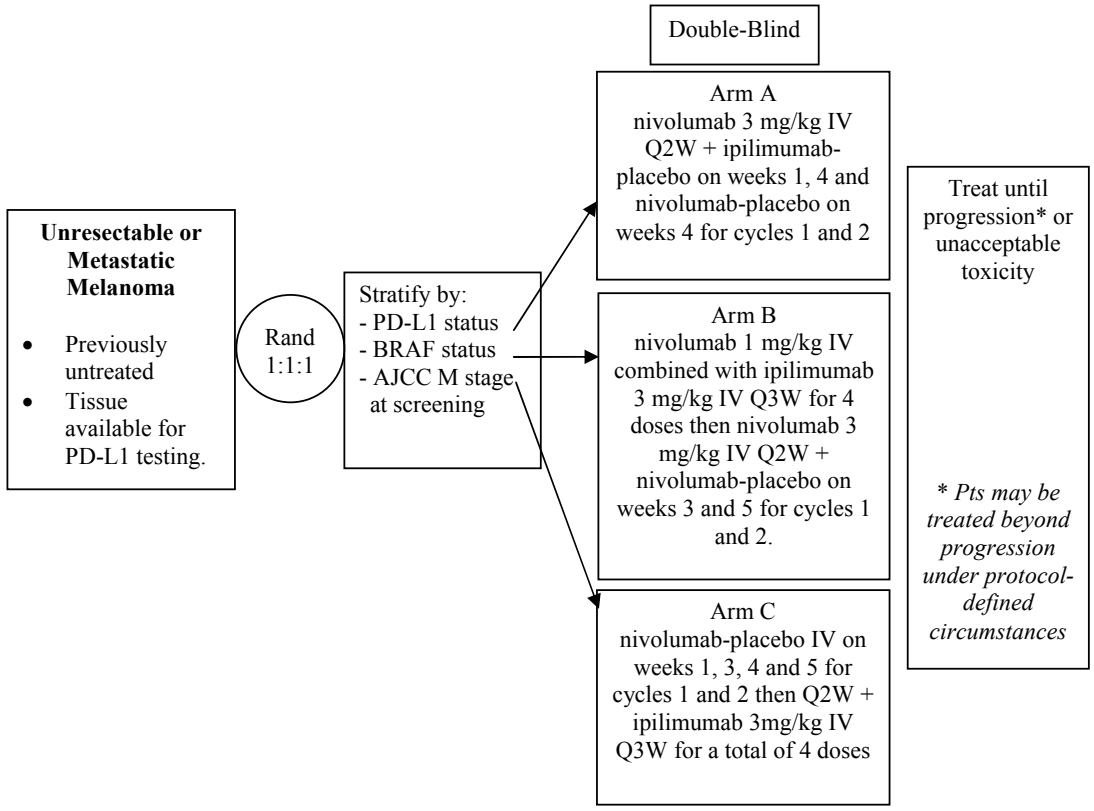
Subjects will be randomized 1:1:1 and stratified by PD-L1 status, BRAF status, and AJCC M stage as described below:

- PD-L1 status
  - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- BRAF status
  - BRAF mutation positive vs
  - BRAF wildtype
- AJCC M stage
  - M0/M1a/M1b vs
  - M1c

PD-L1 status is included as a stratification factor to achieve balance between treatment arms with respect to a potentially prognostic variable. The rationale for selecting the ≥5% expression cut-off is to achieve a 50:50 split (approximately) of PD-L1 positive:PD-L1 negative in the absence of a definitive cut-off. Additionally, this cut-off has been cited in precedent literature reports related to PD-L1 IHC scoring in melanoma, albeit with a different assay[3,4].

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

Once a subject has signed the informed consent form, a subject number will be assigned through an interactive voice response system (IVRS). Every subject that signs an informed consent form must be assigned a subject number in IVRS.

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

Subjects who have been enrolled in IVRS and have met all eligibility criteria will be ready to be randomized through the IVRS. The following information is required for subject randomization:

- Subject number
- Date of birth
- PD-L1 status
- BRAF status

- M Stage

Subjects meeting all eligibility criteria will be randomized in a 1:1:1 ratio to Arm A nivolumab + placebo, Arm B nivolumab + ipilimumab, or Arm C ipilimumab + placebo, stratified by PD-L1 status (positive vs negative/indeterminate), M Stage (M0/M1a/M1b vs M1c), and BRAF status (mutation positive vs wildtype). Randomization procedures will be carried out via permuted blocks within each stratum.

2.3 Blinding and Unblinding

The Sponsor, subjects, investigator, and site staff will be blinded to the study drug administered, except as noted below.

Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

The investigator and subject will be unblinded to the subject's treatment assignment through the IVRS, once the following 2 conditions are met:

1) Documented disease progression, and
2) Discontinuation of blinded study treatment

Subjects may not resume initial study treatment once unblinded.

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.

The Sponsor will remain blinded until the time of final analysis of the primary OS endpoint.The independent DMC may be unblinded to enable review of safety and efficacy reports. Details are specified in the DMC Charter[2].

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

2.4 Protocol Amendments

This SAP incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 02	20-AUG-2013	Included language allowing palliative radiation therapy and

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
(Incorporates Amendment 04)		palliative surgical resection under specific circumstances. Asymptomatic elevations in amylase and lipase not associated with symptoms or clinical manifestations of pancreatitis were removed from the dose delay or discontinuation criteria.

2.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. Following review, the DMC will recommend continuation, modification, or discontinuation of this study based on reported safety and efficacy data. Details of DMC responsibilities and procedures are specified in the DMC charter[2]. Representatives of the Sponsor will serve only as coordinators of the committee, without having full member responsibilities or privileges. In addition, the Sponsor will independently review safety data in a blinded manner during the conduct of this trial to ensure that any safety issues are identified and addressed.

3 OBJECTIVES

3.1 Primary

- To compare OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.

3.2 Secondary

- To compare PFS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To compare ORR of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for OS

- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

3.3 Exploratory

- To evaluate duration of and time to objective response of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab in subjects with unresectable or metastatic melanoma
- To assess the overall safety and tolerability of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab monotherapy in subjects with unresectable or advanced melanoma
- To characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination with nivolumab
- To characterize the immunogenicity of nivolumab and nivolumab combined with ipilimumab
- To evaluate pharmacokinetic drug-drug interaction between nivolumab and ipilimumab
- To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) of nivolumab and/or nivolumab combined with ipilimumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes.
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events
- To assess changes in health status and work and activity impairment in treatment groups using the EuroQoL EQ-5D and the Work Productivity and Activity Impairment questionnaire (WPAI-GH) respectively
- To describe the quality of survival in patients after treatment discontinuation using the EuroQoL EQ-5D .

4 ENDPOINTS

4.1 Primary

4.1.1 Overall Survival

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. The overall survival rate at time T is defined as the probability that a subject is alive at time T following randomization.

4.2 Secondary

4.2.1 Progression Free Survival

PFS is defined as the time from randomization to the date of first documented disease progression, as assessed by the investigator per RECIST 1.1, or death due to any cause,

whichever occurs first. Clinical deterioration in the absence of progression per RECIST 1.1 is not considered progression for the purpose of determining PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The progression free survival rate at time T is defined as the probability that a subject has not progressed and is alive at time T following randomization.

Censoring rules for the primary analysis of PFS are presented in Table 4.2.1-1. Alternate censoring rules for sensitivity analyses are specified in Section 7.5.2.2.

Table 4.2.1-1: Censoring Scheme for Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to initiation of subsequent therapy	Censored
Death without progression	Date of death	Progressed

4.2.2 Objective Response Rate

The ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of progression, as assessed by the investigator per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue

treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

4.2.3 PD-L1 Expression

PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an immunohistochemistry (IHC) assay. Tumor biopsy specimens without measurable PD-L1 expression are classified as indeterminate if the staining is hampered for reasons attributed to the biology of the specimen and not because of improper specimen preparation or handling. Missing specimens, specimens that were not optimally collected, and all other specimens are classified as unknown. Subjects must be classified as PD-L1 positive, PD-L1 negative, or indeterminate (ie not unknown) in order to be randomized.

4.2.4 EORTC-QLQ-C30

Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire Version 3. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups[5]. 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.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual, as follows:

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100

- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: ((Q8-1)/3 * 100
- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. This is the method proposed in the scoring manual. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 4.2.4-1 and included in the analysis. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

Table 4.2.4-1: Time Windows for EORTC-QLQ-C30 Assessments

Nominal Time-Point	Time Window
Week 1 (Baseline)	Prior to first dose on Day 1
Week 5	Day 2 thru Day 36, inclusive
Week 7	Day 37 thru Day 57, inclusive
Week 11	Day 58 thru Day 78, inclusive
Week 13	Day 79 thru Day 99, inclusive
Week 17	Day 100 thru Day 120, inclusive
Week 19	Day 121 thru Day 141, inclusive
Week 23	Day 142 thru Day 162, inclusive
Week 25	Day 163 thru Day 190, inclusive
Every 6 Weeks thereafter	Nominal Day (+21 days/-20days, inclusive)
Follow-Up 1	N/A
Follow-Up 2	N/A

4.3 Exploratory

4.3.1 Duration of Objective Response

Duration of objective response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first disease progression, as assessed by the investigator per RECIST 1.1 or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they were censored for the primary definition of PFS (Table 4.2.1-1). DOR will be evaluated for responders (i.e. subjects with a BOR of CR or PR) only.

4.3.2 Time to Objective Response

Time to Objective Response (TTR) is defined as the time from randomization to the date of the first documented response (CR or PR). TTR will be evaluated in all randomized subjects and for responders (i.e. subjects with a BOR of CR or PR).

4.3.3 Safety

Safety and tolerability will be measured by the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade) in each treatment group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP[1].

4.3.4 Pharmacokinetics

Pharmacokinetics will be measured by serum concentrations of nivolumab and/or ipilimumab. Samples will be collected to characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination.

4.3.5 Immunogenicity

Refer to Core Safety SAP[1].

4.3.6 Biomarkers

Biomarkers potentially associated with clinical endpoints will be measured by analyzing tumor and blood samples. Biomarker endpoints include, but are not limited to, single-nucleotide polymorphisms (SNPs), proteins in tumor specimens and serum, and immune cell populations.

4.3.7 EuroQoL EQ-5D

Subjects' overall health status will be assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L)[6]. EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (i.e., EQ-5D index score) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)[7].

4.3.8 WPAI:GH

The effect of health problems on a subject's ability to work and perform normal daily activities will be assessed using the Work Productivity and Activity Impairment questionnaire: General Health (WPAI:GH)[8].

This questionnaire is a 6-item questionnaire yielding four different types of scores. The WPAI:GH was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work /reduced on-the-job effectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The recall period in all WPAI validation studies is 7 days.

5 SAMPLE SIZE AND POWER

The sample size is calculated to compare OS between nivolumab and ipilimumab and to compare OS between the combination of nivolumab/ipilimumab and ipilimumab at a Type I error level of 0.025 (two-sided) for each comparison. The truncated Hochberg multiple testing procedure[9] will be applied to control the overall Type I error at an alpha of 0.05 (two-sided). Section 7.5.4 describes the testing hierarchy and multiple testing procedure methodology. The number of events and power are calculated assuming an exponential distribution in each treatment group.

Approximately 915 subjects will be randomized to the three treatment arms in a 1:1:1 ratio. For each OS comparison, at least 460 events in the two respective treatment arms provide at least 90% power to detect a hazard ratio (HR) of 0.72 with a type I error of 0.025 (two-sided). The HR of 0.72 corresponds to a 39% increase in the median OS, assuming a median OS of 14 months for ipilimumab and 19.4 months for each of the experimental treatment arms. Assuming the distribution of events follows the alternative hypothesis, approximately 247 events in the control group and 213 in each of the experimental groups are expected.

In time-to-event trials, the final analysis typically occurs when a certain number of events, pooled across treatment arms, are observed such that the trial is adequate powered under the design assumptions. However, in the first-line ipilimumab melanoma trial, CA184-024, the projected trial duration of 34 months was very different from the actual trial duration of 54 months, with the event rate slowing dramatically in the last 18 months[10]. In order that such a phenomenon does not unduly delay the final analysis in the current trial, the analysis of both

primary OS comparisons will be conducted when approximately 247 events (ie deaths) in the control group have been observed. This approach has the added effect of harmonizing the timing of the two comparisons. The independent statistical group supporting DMC activities is charged with tracking the number of events in the control group and alerting the sponsor when the required number of events has been observed for final analysis[2].

At the time of final analysis, the exact number of deaths in an experimental group will depend on the observed hazard ratio. Under a true hazard ratio of 0.72, observing meaningfully fewer than 213 deaths in an experimental group is a low probability outcome and would indicate a greater treatment effect relative to control, thus maintaining adequate power for that comparison.

Assuming a piecewise constant accrual rate (3 subjects during Month 1, 6 subjects during Month 2, 27 subjects/month during Months 3 to 4, 48 subjects/month during Months 5 to 6, 69 subjects/month after Month 6), it will take approximately 44.1 months to obtain the required number of deaths for the final OS analysis (17.0 months for accrual and 27.1 months for survival follow up). It is projected that an observed HR of 0.8114 or less corresponding to a 3.3 month or greater improvement in median OS (14 vs. 17.3 months) for each comparison, would result in a statistically significant improvement in the final analysis of OS.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment) with a measurable result. If all specimens for a given subject are either indeterminate or unknown, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered unknown.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

6.2 Treatment Regimens

The treatment group "**as randomized"** will be retrieved from the IVRS system.

- Arm A: Experimental arm: nivolumab
- Arm B: Experimental arm: nivolumab + ipilimumab
- Arm C: Control arm: ipilimumab

The treatment group "**as treated**" will be the same as the arm as randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 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. This is the primary dataset for analyses of study conduct, study population, and efficacy.
- All Treated Subjects: All subjects who received at least one dose of nivolumab, nivolumab-placebo, ipilimumab, or ipilimumab-placebo. This is the primary dataset for analyses of exposure and safety.
- Response-Evaluable Subjects: All randomized subjects with measurable disease at a baseline tumor assessment and at least one on-treatment tumor assessment.
- All PK Subjects: All subjects with available serum time-concentration data
    - Immunogenicity Subjects:
  - Nivolumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline ipilimumab immunogenicity assessment.
- PD-L1 Measurable Subjects: All subjects with a measurable PD-L1 expression result (ie excludes indeterminate and unknown).

7 STATISTICAL ANALYSES

7.1 General Methods

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum and maximum values. If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions (i.e. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[11] (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals[12]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[13].

The difference in ORRs between the two treatment arms along with their two-sided 95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting[14], adjusting for the stratification factors PD-L1 status, M stage, and BRAF status.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all randomized subjects. Randomization date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

Furthermore, the accrual pattern will be summarized by the stratification factors PD-L1 status, M Stage, and BRAF Status.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by treatment group and overall. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

<u>At Entrance:</u>

- Subjects with baseline ECOG performance status > 1
- Subjects who received prior systemic anti-cancer treatment in the metastatic setting
- Subjects without histologically documented Stage III or Stage IV melanoma, as per AJCC staging system

- Subjects with unknown BRAF V600 status (CRF)

On-study:

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy
- Subjects treated differently than as randomized (subjects who received the wrong treatment, excluding the never treated)

Listings will also be provided.

7.2.3 Unblinding

A summary of subjects whose treatment was unblinded during the course of the study will be provided based on a cumulative unblinding report prepared by a randomization coordinator within BMS. The frequency of subjects unblinded due to medical emergency or pregnancy versus those unblinded due to documented disease progression and decision to discontinue treatment will be reflected in this summary.

7.3 Study Population

Summaries of study population will be based on all randomized subjects, except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed only on the all enrolled population only.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized. This analysis will be performed only on the all randomized population only.

A subject listing for all randomized subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized.

7.3.2 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized by treatment group, as randomized. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)

- Age category I (<65, ≥65)
- Age category II (<65, ≥65- <75, ≥ 75)
- Gender (male, female)
- Race (white, black, asian, other)
- Region (US, EU, Australia, Rest of World)
- ECOG Performance Status (0, 1)
- M Stage at Study Entry (M0, M1a, M1b, M1c) (source: CRF)
- AJCC Stage at Study Entry (III, IV)
- Weight (descriptive statistics)
- PD-L1 Status (positive, negative/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant, wildtype) (source: CRF)
- BRAF mutation test (Cobas+THxID, Other, Unknown)
- Baseline LDH (≤ULN, >ULN)
- Baseline LDH (≤2∗ULN, >2*ULN)
- History of Brain Metastases (Yes, No)
- Time from Initial Disease Diagnosis to Randomization (<1 year,1-<2 year, 2-<3 year,3-<4 year, 4-<5 year, ≥5 year)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

Similarly the following IVRS data will be summarized by treatment group as randomized.

- BRAF mutation status (BRAF mutant/wildtype)
- M Stage at Study Entry (M0/M1a/M1b/M1c)
- PD-L1 Status (positive and negative/indeterminate)

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by treatment group as randomized.

- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to randomization (subjects who received prior adjuvant therapy), (< 6 months and >= 6 months)

- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg neck, cardiovascular, lungs, etc) and by treatment group as randomized.

7.3.6 Discrepancies between IVRS and CRF information

Summary tables (cross-tabulations) by treatment group as randomized for stratification factors will be provided to show any discrepancies between what was reported through IVRS vs. CRF data or clinical database (baseline).

- M Stage at Study Entry (IVRS vs. CRF data)
- PD-L1 status (IVRS vs. clinical database)
- BRAF Status (IVRS vs. CRF data)

7.4 Extent of Exposure

Analyses will be performed by treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28)
- Number of concomitant doses received (nivolumab + ipilimumab-placebo, ipilimumab + nivolumab, and ipilimumab + nivolumab-placebo. A subject will be considered to have received concomitant doses of ipilimumab, and nivolumab or nivolumab-placebo, if both infusions are administered on the same date.

The following parameters will be summarized (descriptive statistics) by study therapy and treatment group:

- Number of doses received (nivolumab and ipilimumab):
- Cumulative dose (nivolumab and ipilimumab)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%. (nivolumab and ipilimumab)

Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab Arm A	Nivolumab Arm B	Ipilimumab Arms B and C
Dosing Schedule per Protocol	3 mg/kg every 2 weeks	1 mg/kg every 3 weeks for 4 doses followed by 3 mg/kg every 2 weeks	3 mg/kg every 3 weeks for 4 doses
Dose	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Cycle Duration$_{(i)}$ (wk)	N/A	(Dose date$_{(i+1)}$ - Dose date$_{(i)}$)/7	N/A
Cycle Intensity$_{(i)}$ (mg/kg/wk)	N/A	Dose$_{(i)}$/Cycle Duration$_{(i)}$	N/A
Relative Cycle Intensity $_{(i)}$ (%)	N/A	(Cycle Intensity$_{(i)}$/intended dose per week) * 100	N/A
Relative Dose Intensity (%)	Cum dose /[(Last dose date - Start dose date + 14) x 3/14] x 100	Sum of all Relative Cycle Intensities divided by N	Cum dose /[(Last dose date - Start dose date + 21) x 3/21] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS. i = 1, 2,...,N, where N = number of infusions. Cycle Duration (N) = 3 weeks for nominal 1 mg/kg nivolumab doses and 2 weeks for nominal 3 mg/kg. Intended dose per week is .33 mg/kg for nominal 1 mg/kg nivolumab doses and 1.5 mg/kg for nominal 3 mg/kg nivolumab doses.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each nivolumab and ipilimumab infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (ie greater than or equal to 4 days from scheduled dosing date) for both nivolumab and ipilimumab. All studies drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of dose delays per subject, length of delay, and reason for delay

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (i.e. on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary table will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing will accompany the table.

7.5 Efficacy

7.5.1 Overall Survival

7.5.1.1 Primary Analysis

OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in all randomized subjects using a truncated Hochberg procedure to address multiplicity (See Section 7.5.4). Hazard ratios (HR) and corresponding two-sided (1-adjusted α)% confidence intervals (CI) will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

Additionally, a descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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

Survival rates at 6, 12, 18, 24, 36, 48 months, and then every year will be estimated using KM estimates on the OS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up)
- off-study: (lost to follow-up, withdrew consent, etc)

To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential nonconstant treatment effect.

7.5.1.2 Sensitivity Analysis

- OS for each of the two experimental arms will be compared to the control group using a two-sided unstratified log-rank test. Estimates of the HRs and corresponding two sided 100(1-α)% CIs will be provided based on a Cox proportional hazards model, with treatment group as a single covariate.
- OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by PD-L1 status (clinical database source), BRAF status (CRF source), and M Stage at screening (CRF source) as determined at baseline. Estimates of the HRs and corresponding two-sided (1-α)% CIs will be provided based on a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

7.5.1.3 Subgroup Analysis

To assess consistency of treatment effects in different subsets, a "forest" plot of the OS unstratified hazard ratios (and 95% CIs) will be produced for the following subgroups.

- PD-L1 Status (positive and negative/indeterminate) (source: clinical database)
    - BRAF mutation status (BRAF mutant and wildtype) (source: CRF)
- M Stage at Study Entry (M0/M1a/M1b and M1c) (source: CRF)
    - Age category I (<65 and ≥65)
    - Age category II (<65, ≥65- <75, and ≥ 75)
    - Gender (male and female)
    - Race (white, black, asian, and other)
    - Region (US, EU, Australia, and Rest of World)
    - Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes and No)
- Smoking Status (Yes and No)
- Baseline LDH (≤ULN and >ULN)
- Baseline LDH (≤2∗ULN and >2*ULN)
- AJCC Stage (III and IV)

If a subgroup category has less than 10 subjects per treatment group, HR will not be computed/displayed.

7.5.1.4 Multivariate Analysis

A multivariate Cox model, stratified by PD-L1 status (clinical database source), BRAF status (CRF source), and M Stage at screening (CRF source) will be fitted to assess the treatment effect on OS when adjusted for potential prognostic factors. The following prognostic factors will be included in the model.

- Age category (<65, ≥65- <75, ≥ 75)
- Gender (male and female)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes, No)
- Baseline LDH (≤ULN, >ULN)

HRs and corresponding 95% CIs will be provided for treatment variable and all covariates.

7.5.1.5 Subject Follow-Up

The extent of follow-up defined as the time between randomization date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all randomized subjects.

The currentness of follow-up, defined as the time between last OS contact (i.e., last known date alive or death date) and data cut-off date, will be summarized by treatment group. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 120-150 days, 151 or more days.

7.5.1.6 Subsequent Therapy

Subsequent therapy and response to subsequent therapy will be summarized and listed.

- Subsequent Therapy
  - Chemotherapy by drug name
  - Hormonal or biologic therapy by drug name
  - Immunotherapy (anti-PD1 agents, anti-PDL1 agents, anti-CTLA4 agents, and others) by drug name
  - BRAF inhibitor by drug name
  - MEK/NRAS inhibitor by drug name
  - Other investigational agent by drug name
  - Surgery
  - Radiotherapy
  - Any combination of the above
- By Subject Listing of Subsequent Therapy

7.5.1.7 Survival by Tumor Response

Exploratory analyses of survival by response category will be analyzed by treatment group using the landmark method[15]. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time. This will assess whether survival from the landmark depends on the subject's response status at the landmark. Subjects who go off protocol (e.g. subjects who die) before the time of landmark will be excluded from the analysis. Additional response categories could be also explored.

The survival curves from Week 12 and Month 6 by response status, for each treatment group will be produced using the KM product-limit method. Two sided, 95% CIs for median OS will be computed.

7.5.2 Progression Free Survival

7.5.2.1 Primary Analysis

PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided (1-adjusted

α)% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

Additionally, a descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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

PFS rates at 6, 12, and 18 months will be estimated using KM estimates on the PFS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated

The source of progression event (death versus progression) will be summarized by treatment group.

The status of subjects who are censored in the PFS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, never treated)
- Received subsequent anticancer therapy

7.5.2.2 Sensitivity Analysis

Similar analyses of PFS will be performed using the following modifications.

- PFS using the strata as determined at baseline (CRF source for M-stage and BRAF status, clinical database for PD-L1) and the censoring scheme for primary analysis Table 4.2.1-1. This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

PFS accounting for tumor assessments occurring on or after initiation of anticancer therapy and censoring scheme 1 for sensitivity analysis (Table 7.5.2.2-1).

PFS accounting for clinical progression, missing tumor assessments prior to PFS event (progression or death) and censoring scheme 2 for sensitivity analysis (Table 7.5.2.2-2).A subject is considered to have two or more missing tumor assessments if the elapsed time between the PFS event and the last assessment prior to the events is greater than 12 weeks + 10 days (94 days).

Table 7.5.2.2-1: Censoring Scheme 1 for Sensitivity Analysis of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1	Progressed

Table 7.5.2.2-1: Censoring Scheme 1 for Sensitivity Analysis of PFS

Situation	Date of Progression of Censoring (excludes clinical progression)	Outcome
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression	Date of death	Progressed

Table 7.5.2.2-2: Censoring Scheme 2 for Sensitivity Analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 or clinical progression	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to initiation of subsequent therapy	Censored
Death without progression	Date of death	Progressed
Death or progression after two or more missed visits	Date of last evaluable tumor assessment prior to the PFS event	Censored

Note: Censoring rule for death after two or missed visits supersedes rule for death without progression, where applicable

7.5.2.3 Subgroup Analysis

To assess consistency of treatment effect in PFS in different subgroups, a 'forest' plot of the PFS unstratified hazard ratios and two-sided 95% CIs will be produced for the same variables as in the OS analysis (see Section 7.5.1.3) If a subgroup category has less than 10 subjects per treatment group, HR will not be computed/displayed.

7.5.3 Objective Response Rate

7.5.3.1 Primary Analysis

ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage at screening to compare each of the two experimental treatments to the control group. Associated odds ratios and (1-adjusted α)% CIs

will be calculated. An estimate of the difference in ORRs and corresponding 95% CI will be using calculated using CMH methodology and adjusted by the same stratification factors.

Additionally, a descriptive odds ratio and estimate of the difference in ORRs, along with corresponding two-sided 95% CIs, will be provided to evaluate differences between the two experimental arms.

ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms. BOR will be tabulated for each treatment group.

7.5.3.2 Sensitivity Analysis

Similar analyses of ORR will be performed using the following modification:

- ORR using the strata as determined at baseline (CRF source for M-stage and BRAF status, clinical database for PD-L1). This analysis will be performed only if the IVRS value for one stratification actor differs from the baseline value in at least 10% of randomized subjects.

7.5.3.3 Subgroup Analysis

To assess consistency of treatment effects in ORR in different subsets, a "forest" plot of the unweighted differences in ORRs and corresponding exact 95% CIs using the method of Agresti and Min[16] will be produced for the following subgroups:

- PD-L1 Status (positive and negative/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant/wildtype) (source: CRF)
- M Stage at Study Entry (M0/M1a/M1b and M1c) (source: CRF)
- Age category (<65, ≥65- <75, ≥ 75)
- Gender (male and female)
- Race (white, black, asian, and other)
- Region (US, EU, Australia, Rest of World)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes, No)
- Baseline LDH (≤ULN, >ULN)
- Baseline LDH (≤2∗ULN, >2*ULN)

If a subgroup category has less than 10 subjects per treatment group, ORR will not be computed/displayed.

7.5.3.4 Duration of Objective Response

DOR curves in each treatment group will be estimated using the KM product-limit method for subjects with a BOR of CR or PR. Median DOR, corresponding two-sided 95% CI, and range will be reported.

7.5.3.5 Time to Objective Response

Summary statistics of TTR will be provided by treatment group for subjects with a BOR of CR or PR. TTR curves will be estimated using the KM product-limit method in all randomized subjects and will represent the cumulative rate of response over time. For non-responders, subjects will be censored at the maximum time of response + 1 day of all subjects in their respective treatment group. Cumulative response rates will be tabulated at Week 12, Month 6, and Month 12.

7.5.4 Testing Hierarchy and Control of the Family-Wise Error Rate (FWER)

7.5.4.1 Testing Hierarchy

In order to preserve the family-wise type I error rate of 5%, a parallel gatekeeping strategy[17] will be applied. Three families of hypotheses in this trial will be tested in the following hierarchical order:

1) Overall Survival Family
   a) Nivolumab monotherapy OS versus Ipilimumab monotherapy OS
   b) Nivolumab combined with Ipilimumab OS versus Ipilimumab monotherapy OS
2) Progression Free Survival Family
   a) Nivolumab monotherapy PFS versus Ipilimumab monotherapy PFS
   b) Nivolumab combined with Ipilimumab PFS versus Ipilimumab monotherapy PFS
3) Objective Response Rate Family
   a) Nivolumab monotherapy ORR versus Ipilimumab monotherapy ORR
   b) Nivolumab combined with Ipilimumab ORR versus Ipilimumab monotherapy ORR

Testing of the progression-free survival family will only occur if at least one comparison is significant in the OS family. Likewise, testing of the ORR family will only occur if at least one comparison is significant in PFS family. If neither comparison is significant in the OS family, no further testing will be performed.

7.5.4.2 Truncated Hochberg Procedure

The truncated Hochberg[18] multiple testing procedure will be used in this study. It will be carried out as follows:

1) Order the two p-values within a family, $p_{(1)} \leq p_{(2)}$
2) The procedure rejects both hypotheses and stops testing if

$$p_{(2)} \leq \qquad ,$$

where γ ($0 \leq \gamma < 1$) is user specified truncation parameter. We will refer to $\left[\gamma + \frac{(1-\gamma)}{2}\right]\alpha$ as the critical constant for comparing $p_{(2)}$.

3) If $p_{(2)}$ is not significant, $p_{(1)}$ is compared to $\alpha/2$.

If both hypotheses are rejected, the full amount of α will be carried forward to the next family of hypotheses. If only $p_{(1)}$ is rejected, the amount of α carried forward to next family of hypotheses is equal to $\alpha - \left[\gamma + \frac{(1-\gamma)}{2}\right]\alpha$.

7.5.4.3 Testing Strategy

Overall Survival Family

The first family to be tested will be OS. For this comparison the truncation parameter will be set to 0.8, resulting in a critical constant of 0.045. The truncation parameter was selected with the goal of keeping the critical constant as close to 0.05 as possible while maintaining adequate alpha to carry forward if only one hypothesis is rejected. In that case, the next family of hypotheses will be tested at the α = 0.005 level. If both OS hypotheses are rejected, the next family will be tested at the α = 0.05 level.

Progression Free Survival Family

The next family to be tested will be PFS. Regardless of the amount of alpha carried forward, the truncated Hochberg MTP will be used for this family. The table below gives the approximate power for various levels of α.

Table 7.5.4.3-1: Power Calculations for PFS

α	0.0001	0.0005	0.001	0.002	0.003	0.004	0.005
Approx. Power	68%	81%	86%	90%	92%	93%	94.2%

The power calculations assume a median PFS time of 3 months in the control (Ipilimumab monotherapy) arm with a hazard ratio of 0.7, resulting in a median PFS time of 4.3 months for each treatment arm.

If both OS comparisons are significant then α = 0.05 will be used on this family. A truncation parameter of 0.6 will be used, resulting in comparing the largest p-value to 0.04 and (if the largest p-value is not significant) comparing the smallest p-value to 0.025.

If only one OS comparison is significant then α = 0.005 will be used on this family. The truncated Hochberg MTP will again be used, but with a truncation parameter set to 0.6. Under this scenario, the largest p-value for comparing PFS will be compared to $\left[0.6 + \frac{(1-0.6)}{2}\right] 0.005 = 0.004$. If this is not significant, the smallest p-value will be compared to 0.0025. From the above table, both comparisons will have an approximate power of greater than 90%.

Objective Response Family

The final family to be tested will be ORR. The regular (non-truncated) Hochberg procedure[19] will be used for this family. The smallest possible alpha to be used for this family is α = 0.001

which corresponds to only one OS and only one PFS comparison being significant. Various power calculations are presented below.

Table 7.5.4.3-2: Power Calculations for ORR

α	0.0001	0.0005	0.001	0.002	0.003	0.004	0.005
Power	83.7%	91.6%	94.3%	96.3%	97.2%	97.7%	98.1%

The power calculations were done assuming 305 subjects per arm and a response rate of 10% in the control (Ipilimumab monotherapy) arm and a 25% response rate in the two experimental treatment arms. Fisher's exact test was used.

Even under the worst case scenario, which would entail comparing the largest p-value to 0.001 and if that is not significant comparing the smallest p-value to 0.0005, we still have greater than 90% power for ORR.

7.5.5 Other Efficacy Analyses

The following subject-level graphics will be provided by treatment group, as randomized.

- For responders only, the time course of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response-evaluable subjects, a waterfall plot showing the best reduction in target lesion tumor burden based on investigator assessment.

7.5.6 Interim Analysis

Not applicable.

7.6 Safety

7.6.1 Deaths

See CORE Safety SAP[1].

7.6.2 Serious Adverse Events

See CORE Safety SAP[1].

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See CORE Safety SAP[1].

7.6.4 Adverse Events Leading to Dose Modification

See CORE Safety SAP[1].

7.6.5 Adverse Events

See CORE Safety SAP[1].

7.6.6 Multiple Events

See CORE Safety SAP[1].

7.6.7 Select Adverse Events

See CORE Safety SAP[1].

7.6.8 Immune Modulating Medication

See CORE Safety SAP[1].

7.6.9 Clinical Laboratory Evaluations

7.6.9.1 Hematology

See CORE Safety SAP[1].

7.6.9.2 Serum Chemistry

Amylase and lipase will be summarized in addition to the serum chemistry parameters described in the CORE Safety SAP[1].

7.6.10 Vital Signs and Pulse Oximetry

See CORE Safety SAP[1].

7.6.11 Immunogenicity

Immunogenicity analyses will be performed separately for Nivolumab ADA Evaluable Subjects and Ipilimumab ADA Evaluable Subjects. See CORE Safety SAP[1].

7.6.12 Pregnancy

See CORE Safety SAP[1].

7.6.13 Clinical Safety Program

See CORE Safety SAP[1].

8 PHARMACOKINETICS

The concentration vs. time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug- drug interaction between nivolumab and ipilimumab will

be studied by population PK approach. Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately.

9 BIOMARKERS

BRAF mutation status is embedded within the study design with analyses described in preceding sections. PD-L1 expression is being studied as a predictive biomarker in several other nivolumab melanoma studies including, but not limited to, CA209037, CA209066, and CA209069. Primary endpoint analyses for these studies are projected to occur prior to CA209067 meeting its final OS analysis. Under such timelines, learnings from the analysis of PD-L1 data in any or all of these studies will be used to define PD-L1 analyses in this study. These analyses, as well as those of exploratory biomarkers, will be documented in a separate statistical analysis plan and may be reported external to the clinical study report.

10 OUTCOMES RESEARCH

Additional analysis of outcomes research endpoints, including EuroQoL EQ-5D and WPAI:GH, will be described in a separate analysis plan and presented outside of the clinical study report.

10.1.1 EORTC-QLQ-C30

Baseline measures will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale by treatment group, based on all randomized subjects with a baseline measurement.

Change from baseline will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale at each assessment time point by treatment group. This analysis will be performed in all randomized subjects who have an assessment at baseline and at least one on-study assessment.

EORTC-QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point by treatment group.

11 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[20].

Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification [21].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive +1 day and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive + 1 day
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive + 1 day

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (e.g. time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

12 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

13 REFERENCES

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[20] Adverse Event Domain Requirements Specification. Bristol-Myers Squibb Co. PRI. Version 2.1. April 23, 2012.

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STATISTICAL ANALYSIS PLAN FOR CLINICAL STUDY REPORT

A PHASE 3, RANDOMIZED, DOUBLE-BLIND STUDY OF NIVOLUMAB MONOTHERAPY OR NIVOLUMAB COMBINED WITH IPILIMUMAB VERSUS IPILIMUMAB MONOTHERAPY IN SUBJECTS WITH PREVIOUSLY UNTREATED UNRESECTABLE OR METASTATIC MELANOMAPROTOCOL(S)

CA209067

VERSION # 3.0

Approved v9.0 930075901 9.0

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1 BACKGROUND AND RATIONALE

CA209067 (CheckMate 067, CHECKpoint pathway and nivoluMAb clinical Trial Evaluation) is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma. Ipilimumab was chosen as the comparator because it is FDA and EMA approved in subjects with unresectable or metastatic melanoma and currently utilized for previously untreated melanoma patients in the US. It is the only FDA or EMA approved therapy for unresectable or metastatic melanoma that has demonstrated overall survival benefit in a randomized Phase 3 trial that is not BRAF mutational status restricted. Nivolumab monotherapy was chosen as one of the experimental arms because of a favorable risk-benefit ratio assessed in the large Phase 1 study (MDX1106-03/CA209003). The combination of nivolumab and ipilimumab was chosen as an experimental arm because of the preliminary evidence from the Phase 1 study CA209004 suggesting synergy between nivolumab and ipilimumab resulting in a higher frequency of patients with increased magnitude of tumor burden reduction. Evaluating both nivolumab monotherapy and the combination of nivolumab and ipilimumab will provide clinical data allowing clinicians to select the appropriate treatment for each patient based on their individual risk-benefit ratio.

This document contains descriptions of the statistical analyses that will be conducted for the Clinical Study Report (CSR) of study CA209-067. This document also refers to Core Safety Statistical Analysis Plan[1] that contains program level safety analyses descriptions.

Research Hypothesis:

Treatment with nivolumab monotherapy or nivolumab combined with ipilimumab will improve progression free survival and overall survival when compared to ipilimumab monotherapy in previously untreated subjects with unresectable or metastatic melanoma.

Schedule of Analyses:

PFS and OS are co-primary endpoints for this study; each endpoint will be compared 1) between nivolumab and ipilimumab and 2) between nivolumab combined with ipilimumab and ipilimumab.

Formal analyses of PFS and OS will be conducted at different timepoints.

- The PFS analysis is targeted to occur after all subjects have 9 months follow-up per sample size and power considerations (Section 5.1). However, the required minimum follow-up for analysis of PFS is 6 months.
- The OS analysis is targeted to occur after all subjects have 28 months follow-up per sample size and power considerations (Section 5.2). However, the required minimum follow-up for analysis of OS is 22 months.

An independent Data Monitoring Committee (DMC) will monitor the formal PFS analysis and have access to periodic interim safety and efficacy reports to allow for a risk/benefit assessment. At the time of PFS analysis, PFS results and other available safety and efficacy data will be reviewed by the DMC. Communication of PFS results and subsequent potential unblinding to

sponsor will follow guidelines specified in the DMC Charter. Details are specified in the DMC Charter[2].

2 STUDY DESCRIPTION

2.1 Study Design

This is a phase 3, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must have unresectable Stage III or stage IV melanoma, as per the AJCC staging system, and must not have received prior systemic therapy for the treatment of unresectable or metastatic melanoma. Prior adjuvant or neoadjuvant therapy is allowed in the setting of completely resectable disease. PD-L1 status will be obtained by immunohistochemical (IHC) staining of PD-L1 protein prior to randomization.

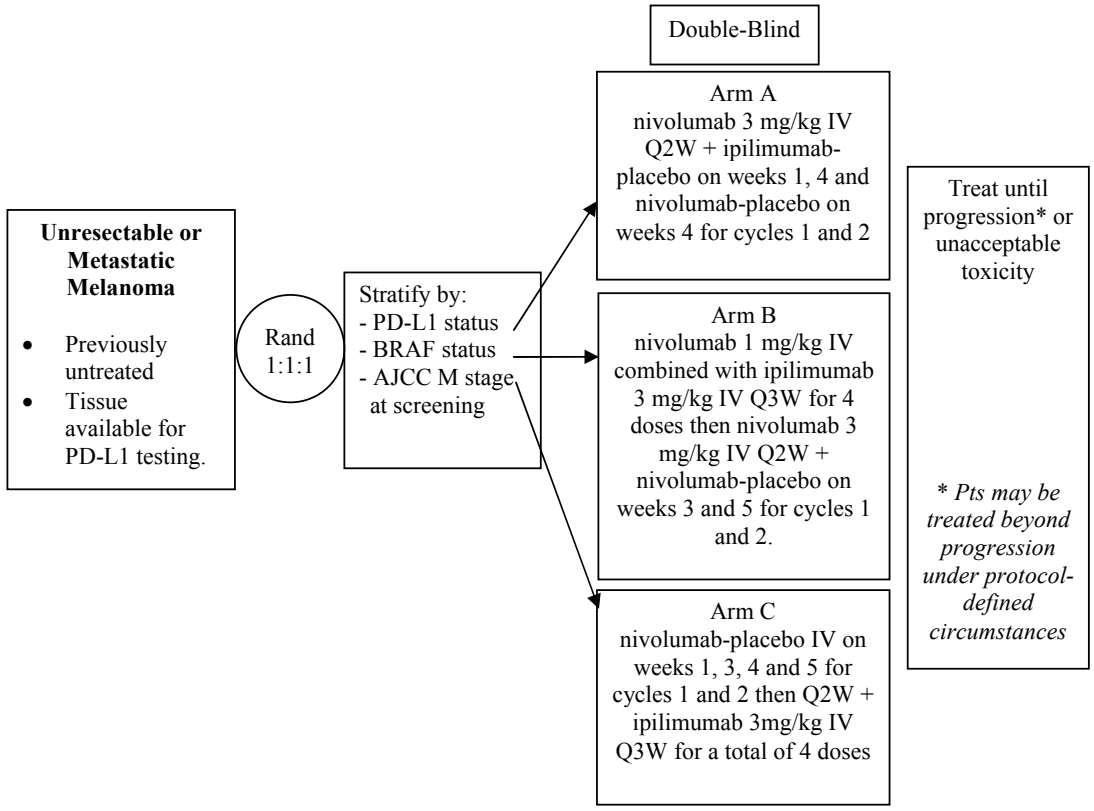
Subjects will be randomized 1:1:1 and stratified by PD-L1 status, BRAF status, and AJCC M stage as described below:

- PD-L1 status
  - PD-L1 positive (≥ 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells) vs
  - PD-L1 negative (< 5% tumor cell membrane staining in a minimum of a hundred evaluable tumor cells)/indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
- BRAF status
  - BRAF mutation positive vs
  - BRAF wildtype
- AJCC M stage
  - M0/M1a/M1b vs
  - M1c

PD-L1 status is included as a stratification factor to achieve balance between treatment arms with respect to a potentially prognostic variable. The rationale for selecting the ≥ 5% expression cut-off is to achieve a 50:50 split (approximately) of PD-L1 positive:PD-L1 negative in the absence of a definitive cut-off. Additionally, this cut-off has been cited in precedent literature reports related to PD-L1 IHC scoring in melanoma, albeit with a different assay[3,4].

The study design schematic is presented in Figure 2.1-1.

Figure 2.1-1: Study Design Schematic



2.2 Treatment Assignment

Once a subject has signed the informed consent form, a subject number will be assigned through an interactive voice response system (IVRS). Every subject that signs an informed consent form must be assigned a subject number in IVRS.

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

Subjects who have been enrolled in IVRS and have met all eligibility criteria will be ready to be randomized through the IVRS. The following information is required for subject randomization:

- Subject number
- Date of birth

- PD-L1 status
- BRAF status
- M Stage

Subjects meeting all eligibility criteria will be randomized in a 1:1:1 ratio to Arm A nivolumab + placebo, Arm B nivolumab + ipilimumab, or Arm C ipilimumab + placebo, stratified by PD-L1 status (positive vs negative/indeterminate), M Stage (M0/M1a/M1b vs M1c), and BRAF status (mutation positive vs wildtype). Randomization procedures will be carried out via permuted blocks within each stratum.

2.3 Blinding and Unblinding

The Sponsor, subjects, investigator, and site staff will be blinded to the study drug administered, except as noted below.

Each investigative site must assign an unblinded pharmacist/designee, and an unblinded site monitor will be assigned to provide oversight of drug supply and other unblinded study documentation.

The investigator and subject will be unblinded to the subject's treatment assignment through the IVRS, once the following 2 conditions are met:

1) Documented disease progression, and
2) Discontinuation of blinded study treatment

Subjects may not resume initial study treatment once unblinded.

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.

The Sponsor will remain blinded until final PFS results are unblinded following guidelines specified in the DMC Charter or until final analysis of the OS endpoint, whichever occurs first. The independent DMC may be unblinded to enable review of safety and efficacy reports. Details are specified in the DMC Charter[2].

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

2.4 Protocol Amendments

This SAP incorporates the following amendments:

Table 2.4-1: Protocol Amendments

Amendment	Date of Issue	Summary of Major Changes
Revised Protocol 02 (Incorporates Amendment 04)	20-AUG-2013	Included language allowing palliative radiation therapy and palliative surgical resection under specific circumstances. Asymptomatic elevations in amylase and lipase not associated with symptoms or clinical manifestations of pancreatitis were removed from the dose delay or discontinuation criteria.
Revised Protocol 03 (Incorporates Amendment 06)	27-JUN-2014	Statistical analysis plan updated to account for the addition of progression free survival as a co-primary endpoint.

2.5 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) has been established to provide oversight of safety and efficacy considerations, study conduct, and risk-benefit ratio. Following review, the DMC will recommend continuation, modification, or discontinuation of this study based on reported safety and efficacy data. Details of DMC responsibilities and procedures are specified in the DMC charter[2]. Representatives of the Sponsor will serve only as coordinators of the committee, without having full member responsibilities or privileges. In addition, the Sponsor will independently review safety data in a blinded manner during the conduct of this trial to ensure that any safety issues are identified and addressed.

3 OBJECTIVES

3.1 Primary

- To compare PFS and OS of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with previously untreated, unresectable or metastatic melanoma.

3.2 Secondary

- To compare ORR of nivolumab monotherapy to ipilimumab monotherapy and that of nivolumab combined with ipilimumab to ipilimumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate differences in OS, PFS, and ORR between nivolumab combined with ipilimumab and nivolumab monotherapy in subjects with unresectable or metastatic melanoma
- To evaluate whether PD-L1 expression is a predictive biomarker for PFS and OS
- To evaluate Health Related Quality of Life (HRQoL) as assessed by the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30

3.3 Exploratory

- To evaluate duration of and time to objective response of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab in subjects with unresectable or metastatic melanoma
- To assess the overall safety and tolerability of nivolumab monotherapy, nivolumab combined with ipilimumab, and ipilimumab monotherapy in subjects with unresectable or advanced melanoma
- To characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination with nivolumab
- To characterize the immunogenicity of nivolumab and nivolumab combined with ipilimumab
- To evaluate pharmacokinetic drug-drug interaction between nivolumab and ipilimumab
- To explore potential biomarkers associated with clinical efficacy (ORR, PFS and OS) of nivolumab and/or nivolumab combined with ipilimumab by analyzing biomarker measures within the tumor microenvironment and periphery (eg, blood, serum, PBMCs) in comparison to clinical outcomes.
- To assess the effects of natural genetic variation (SNPs) in select genes including, but not limited to, PD-1, PD-L1, PD-L2, and CTLA-4 on clinical endpoints and/or on the incidence of adverse events
- To assess changes in health status and work and activity impairment in treatment groups using the EuroQoL EQ-5D and the Work Productivity and Activity Impairment questionnaire (WPAI-GH) respectively
- To describe the quality of survival in patients after treatment discontinuation using the EuroQoL EQ-5D .

4 ENDPOINTS

4.1 Primary

4.1.1 Progression Free Survival

PFS is defined as the time from randomization to the date of first documented disease progression, as assessed by the investigator per RECIST 1.1, or death due to any cause, whichever occurs first. Clinical deterioration in the absence of progression per RECIST 1.1 is not considered progression for the purpose of determining PFS. Subjects who die without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were randomized. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The progression free survival rate at time T is defined as the probability that a subject has not progressed and is alive at time T following randomization.

Censoring rules for the primary analysis of PFS are presented in Table 4.1.1-1. Alternate censoring rules for sensitivity analyses are specified in Section 7.5.1.2.

Table 4.1.1-1: Censoring Scheme for Primary Definition of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to initiation of subsequent therapy	Censored
Death without progression	Date of death	Progressed

4.1.2 Overall Survival

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. The overall survival rate at time T is defined as the probability that a subject is alive at time T following randomization.

4.2 Secondary

4.2.1 Objective Response Rate

The ORR is defined as the number of subjects with a best overall response (BOR) of a complete response (CR) or partial response (PR) divided by the number of randomized subjects for each treatment group. The BOR is defined as the best response designation, as determined by the investigator, recorded between the date of randomization and the date of progression, as assessed by the investigator per RECIST 1.1 or the date of subsequent anticancer therapy (including tumor-directed radiotherapy and tumor-directed surgery), whichever occurs first. For subjects without evidence of RECIST 1.1 progression or subsequent anticancer therapy, all available response designations will contribute to the BOR assessment. For subjects who continue treatment beyond progression, the BOR will be determined based on response designations up to the time of initial RECIST 1.1 progression.

4.2.2 PD-L1 Expression

PD-L1 expression is defined as the percent of tumor cells demonstrating plasma membrane PD-L1 staining of any intensity using an immunohistochemistry (IHC) assay. Tumor biopsy specimens without measurable PD-L1 expression are classified as indeterminate if the staining is hampered for reasons attributed to the biology of the specimen and not because of improper specimen preparation or handling. Missing specimens, specimens that were not optimally collected, and all other specimens are classified as unknown. Subjects must be classified as PD-L1 positive, PD-L1 negative, or indeterminate (ie not unknown) in order to be randomized.

4.2.3 EORTC-QLQ-C30

Health-related quality of life (HRQoL) will be assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire Version 3. It is a 30-item instrument that has gained wide acceptance in oncology clinical studies. The EORTC QLQ-C30 is composed of multi-item and single scales. These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups[5]. 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.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual, as follows:

Functional scales:

- Physical functioning: (1 - ((Q1+Q2+Q3+Q4+Q5)/5 -1)/3) * 100
- Role functioning: (1 - ((Q6+Q7)/2-1)/3) * 100
- Emotional functioning: (1 - ((Q21+Q22+Q23+Q24)/4-1)/3) * 100
- Cognitive functioning: (1 - ((Q20+Q25)/2-1)/3) * 100
- Social functioning: (1 - ((Q26+Q27)/2-1)/3) * 100

Global health status:

- Global health status/QoL: ((Q29+Q30)/2-1)/6 * 100

Symptom scales/items:

- Fatigue: ((Q10+Q12+Q18)/3-1)/3 * 100
- Nausea and vomiting: ((Q14+Q15)/2-1)/3 * 100
- Pain: ((Q9+Q19)/2-1)/3 * 100
- Dyspnea: ((Q8-1)/3 * 100

- Insomnia: (Q11-1)/3 * 100
- Appetite loss: (Q13-1)/3 * 100
- Constipation: (Q16-1)/3 * 100
- Diarrhea: (Q17-1)/3 * 100
- Financial difficulties: (Q28-1)/3 * 100

Missing values will be imputed for missing items by "assuming that the missing items have values equal to the average of those items which are present" for any scale in which at least half the items are completed. A scale in which less than half of the items are completed will be treated as missing. This is the method proposed in the scoring manual. A questionnaire will be considered as received if at least one of the 15 scales is non-missing (after imputation).

All questionnaires completed at baseline and on-study will be assigned to a time-point according to the windowing criteria in Table 4.2.3-1 and included in the analysis. In case a subject has two on-study assessments within the same window, the assessment closest to the time-point will be used. And, in the case of two assessments at a similar distance to the time-point, the latest one will be chosen. In the event where the subject has no assessment at all in a specific window, the observation will be treated as missing for that time-point.

Table 4.2.3-1: Time Windows for EORTC-QLQ-C30 Assessments

Nominal Time-Point	Time Window
Week 1 (Baseline)	Prior to first dose on Day 1
Week 5	Day 2 thru Day 36, inclusive
Week 7	Day 37 thru Day 57, inclusive
Week 11	Day 58 thru Day 78, inclusive
Week 13	Day 79 thru Day 99, inclusive
Week 17	Day 100 thru Day 120, inclusive
Week 19	Day 121 thru Day 141, inclusive
Week 23	Day 142 thru Day 162, inclusive
Week 25	Day 163 thru Day 190, inclusive
Every 6 Weeks thereafter	Nominal Day (+21 days/-20days, inclusive)
Follow-Up 1	N/A
Follow-Up 2	N/A

4.3 Exploratory

4.3.1 Duration of Objective Response

Duration of objective response (DOR) is defined as the time between the date of first documented response (CR or PR) to the date of the first disease progression, as assessed by the

investigator per RECIST 1.1 or death due to any cause, whichever occurs first. For subjects who neither progress nor die, the duration of objective response will be censored at the same time they were censored for the primary definition of PFS (Table 4.1.1-1). DOR will be evaluated for responders (i.e. subjects with a BOR of CR or PR) only.

4.3.2 Time to Objective Response

Time to Objective Response (TTR) is defined as the time from randomization to the date of the first documented response (CR or PR). TTR will be evaluated in all randomized subjects and for responders (i.e. subjects with a BOR of CR or PR).

4.3.3 Safety

Safety and tolerability will be measured by the incidence of deaths, adverse events, serious adverse events, adverse events leading to discontinuation, adverse events leading to dose delay, select adverse events and specific laboratory abnormalities (worst grade) in each treatment group. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. See details in the Core Safety SAP[1].

4.3.4 Pharmacokinetics

Pharmacokinetics will be measured by serum concentrations of nivolumab and/or ipilimumab. Samples will be collected to characterize pharmacokinetics of nivolumab and ipilimumab administered alone or in combination.

4.3.5 Immunogenicity

Refer to Core Safety SAP[1].

4.3.6 Biomarkers

Biomarkers potentially associated with clinical endpoints will be measured by analyzing tumor and blood samples. Biomarker endpoints include, but are not limited to, single-nucleotide polymorphisms (SNPs), proteins in tumor specimens and serum, and immune cell populations.

4.3.7 EuroQoL EQ-5D

Subjects' overall health status will be assessed using the EuroQol Group's self-reported health status measure (EQ-5D-3L)[6]. EQ-5D essentially has 2 components- the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. Once the data have been collected and a database created, a scoring function can be used to assign a value (ie, EQ-5D index score) to self-reported health states from a set of population-based preference weights.

The EQ VAS records the subject's self-rated health state on a 100-point vertical, visual analogue scale (0 = worst imaginable health state; 100 = best imaginable health state)[7].

4.3.8 WPAI:GH

The effect of health problems on a subject's ability to work and perform normal daily activities will be assessed using the Work Productivity and Activity Impairment questionnaire: General Health (WPAI:GH)[8].

This questionnaire is a 6-item questionnaire yielding four different types of scores. The WPAI:GH was created as a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work /reduced on-the-job effectiveness), work productivity (overall work impairment/absenteeism plus presenteeism) and daily activity impairment attributable to general health. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes. The recall period in all WPAI validation studies is 7 days.

5 SAMPLE SIZE AND POWER

Approximately 915 subjects will be randomized to three treatment arms in a 1:1:1 ratio. The sample size of the study accounts for the co-primary endpoints of progression-free survival (PFS) and overall survival (OS), with an alpha allocation of 0.01 for PFS and 0.04 for OS.

Formal analyses of PFS and OS will be conducted at different timepoints.

- The PFS analysis is targeted to occur after all subjects have 9 months follow-up per sample size and power considerations (Section 5.1). However, the required minimum follow-up for analysis of PFS is 6 months.
- The OS analysis is targeted to occur after all subjects have 28 months follow-up per sample size and power considerations (Section 5.2). However, the required minimum follow-up for analysis of OS is 22 months.

In time-to-events trials, the number of events and power may typically be calculated assuming an exponential distribution in each treatment arm. However for PFS, a delayed separation in curves may be observed in this study as a result of the first tumor assessment being scheduled for Week 12. In addition, a meaningful number of long term survivors have been reported in clinical studies that evaluated immuno-oncologic therapy and such a phenomenon was present in the pivotal first-line ipilimumab Phase 3 studies MDX010-20 and CA184024. As a consequence, the survival curves in this study may not follow an exponential decay and a flattening of the curves may be observed toward the end of this study. Therefore to provide more accurate calculations, the number of events and power are calculated using statistical models based on PFS and OS data external to this study, as noted below.

A piecewise constant accrual rate (30 subjects during Months 1 and 2, 75 subjects during Month 3, 120 subjects during Month 4, 150 subjects during Month 5, 375 subjects during Month 6, 45 subjects during Month 7, and 90 subjects during Month 8) is assumed. Approximately 8 months is required to enroll the required number of subjects.

5.1 Progression Free Survival

For each PFS comparison, the number of events projected to be observed at 9 months follow-up provide approximately 83% power to detect an average hazard ratio (HR) of 0.71 with a Type I

error of 0.005 (two-sided). This modeling assumes PFS medians of 2.8 and 3.1 months, 6 month PFS rates of 21.6% and 36.9%, and 12 month PFS rates of 12.8% and 26.9% in the control arm and experimental arms, respectively. Assuming the distribution of events follows the alternative hypothesis, approximately 266 PFS events in the control group and 223 PFS events in each of the experimental groups are expected at the time of analysis. Calculations are based on statistical models using PFS data from study MDX010-20 for the control arm and PFS data from study CA209038 for the experimental arms.

For the control arm, a mixture of two log-logistic distributions with a cure rate was used to model the PFS distribution. The model for the PFS function is:

$$S(t) = p + (1-p) * \left\{ q * \left(\frac{1}{1 + \left(\frac{t}{\alpha}\right)^{\beta}} \right) + (1-q) * \left(\frac{1}{1 + \left(\frac{t}{\mu}\right)^{\delta}} \right) \right\}$$

The parameters for the ipilimumab model are: p = 0.07265, q = 0.54892, α = 3.47277, β = 1.69551, μ = 2.74808, and δ = 25.5568.

For each experimental arm, we assumed there was a delayed separation of the curve from the control arm. For the first 2.8 months, the control and experimental curves are assumed to have the same distribution given above. After 2.8 months, each experimental arm will again follow a mixture of two log-logistic distributions with a cure rate. The parameters for this model are p = 0.1733, q = 0.6993, α = 3.6807, β = 1.3673, μ = 1.740, and δ = 21.8329. Simulations were employed to calculate the power and hazard ratio.

5.2 Overall Survival

For each OS comparison, the number of events projected to be observed at 28 months of follow-up provide approximately 99% power to detect an average HR of 0.65 with a Type I error of 0.02 (two-sided). This modeling assumes OS medians of 10.2 and 17.2 months, 12 month OS rates of 43.9% and 62.1%, and 24 month OS rates of 24.4% and 39.6% in the control arm and experimental arms, respectively. . Assuming the distribution of events follows the alternative hypothesis, approximately 240 OS events in the control group and 202 OS events in each of the experimental groups are expected at the time of analysis. Calculations are based on statistical models using OS data from study MDX010-20 for the control arm and OS data from study CA209003 for the experimental arms.

For the control arm the following cure rate Weibull model was used:

$$S(t) = p + (1-p) * e^{-\omega t^{\alpha}}$$

The parameters for the control arm model are: p = 0.197, ω = 0.0542, and α = 1.24655. The parameters for the experimental arms are: p = 0.285, ω = 0.0299, and α = 1.30. Simulations were employed to calculate the power and hazard ratio.

6 STUDY PERIODS, TREATMENT REGIMENS AND POPULATIONS FOR ANALYSES

6.1 Study Periods

6.1.1 Baseline Period

Baseline evaluations or events will be defined as evaluations or events that occur before the date and time of the first dose of study treatment.

In cases where the time (onset time of event or evaluation time and dosing time) is missing or not collected, the following definitions will apply:

- Pre-treatment AEs will be defined as AEs with an onset date prior to but not including the day of the first dose of study treatment
- Baseline evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations with a date on or prior to the day of first dose of study treatment

If there are multiple valid assessments, the assessment that is closest to day (and time if collected) of the first dose of study treatment will be used as the baseline in the analyses. If multiple assessments are collected at the same date (and time if collected), the assessment with the latest database entry date (and time if collected) will considered as baseline.

If more than one tumor biopsy specimen is available, baseline PD-L1 expression will be determined from the most recently collected specimen (prior to first dose of study treatment) with a measurable result. If all specimens for a given subject are either indeterminate or unknown, then the PD-L1 expression will be considered indeterminate as long as at least one specimen is indeterminate. Otherwise, PD-L1 expression will be considered unknown.

6.1.2 Post Baseline Period

On-treatment AEs will be defined as AEs with an onset date-time on or after the date-time of the first dose of study treatment (or with an onset date on or after the day of first dose of study treatment if time is not collected or is missing). An AE will be counted as on-treatment if the event occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

On-treatment evaluations (laboratory tests, pulse oximetry and vital signs) will be defined as evaluations taken after the day (and time, if collected and not missing) of first dose of study treatment. An evaluation will be counted as on-treatment if it occurred within 30 days (or 100 days depending on analysis) of the last dose of study treatment.

6.2 Treatment Regimens

The treatment group "**as randomized"** will be retrieved from the IVRS system.

- Arm A: Experimental arm: nivolumab
- Arm B: Experimental arm: nivolumab + ipilimumab

- Arm C: Control arm: ipilimumab

The treatment group "**as treated**" will be the same as the arm as randomized by IVRS. However, if a subject received the incorrect drug for **the entire period** of treatment, the subject's treatment group will be defined as the incorrect drug the subject actually received.

6.3 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. This is the primary dataset for analyses of study conduct, study population, and efficacy.
- All Treated Subjects: All subjects who received at least one dose of nivolumab, nivolumab-placebo, ipilimumab, or ipilimumab-placebo. This is the primary dataset for analyses of exposure and safety.
- Response-Evaluable Subjects: All randomized subjects with measurable disease at a baseline tumor assessment and at least one on-treatment tumor assessment.
- All PK Subjects: All subjects with available serum time-concentration data
- Immunogenicity Subjects:
  - Nivolumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline pre-infusion nivolumab immunogenicity assessment.
  - Ipilimumab ADA Evaluable Subjects: all treated subjects with baseline and at least 1 postbaseline pre-infusion ipilimumab immunogenicity assessment.
- All PD-L1 tested subjects: Randomized subjects who had a tumor biopsy specimen assessed for PD-L1 expression. This will be used for analyses of PD-L1 expression
- All PD-L1 evaluable subjects: All PD-L1 tested subjects with quantifiable PD-L1 expression
- All treated, PD-L1 tested subjects: All PD-L1 tested subjects who received at least one dose of study treatment

7 STATISTICAL ANALYSES

7.1 General Methods

Formal analyses of PFS and OS will be conducted at different time points with PFS being analyzed first (PFS analysis timepoint) followed by analysis of OS (OS analysis timepoint). Except where otherwise noted, analyses will be conducted at both timepoints.

Unless otherwise noted, the bulleted titles in the following subsections describe tabulations of discrete variables, by the frequency and proportion of subjects falling into each category, grouped by treatment (with total). Percentages given in these tables will be rounded and, therefore, may not always sum to 100%. Continuous variables will be summarized by treatment group (with total) using the mean, standard deviation, median, minimum and maximum values.

If a missing category is not being presented in the data display, only those subjects with non-missing values for the parameter being assessed are included in the percentage calculation.

Time to event distributions (i.e. progression free survival, overall survival, time to response, and duration of response) will be estimated using Kaplan Meier techniques. When appropriate, the median along with 95% CI will be estimated based on Brookmeyer and Crowley methodology[9] (using log-log transformation for constructing the confidence intervals). Rates at fixed timepoints (e.g. OS at 12 months) will be derived from the Kaplan Meier estimate along with their corresponding log-log transformed 95% confidence intervals[10]. Confidence intervals for binomial proportions will be derived using the Clopper-Pearson method[11].

The difference in ORRs between the two treatment arms along with their two-sided 95% CI will be estimated using the following Cochran-Mantel-Haenszel (CMH) method of weighting[12], adjusting for the stratification factors PD-L1 status, M stage, and BRAF status.

7.2 Study Conduct

7.2.1 Accrual

The accrual pattern will be summarized per country, investigational site, and per month for all randomized subjects. Randomization date, first dosing date, country, investigational site will be presented in a by subject listing of accrual.

Furthermore, the accrual pattern will be summarized by the stratification factors PD-L1 status, M Stage, and BRAF Status.

7.2.2 Relevant Protocol Deviations

The following programmable deviations will be considered as relevant protocol deviations and summarized by treatment group and overall. Non-programmable relevant eligibility and on-treatment protocol deviations, as well as significant (both programmable and non-programmable) eligibility and on-treatment protocol deviations will be reported through ClinSIGHT listings.

<u>At Entrance:</u>

- Subjects with baseline ECOG performance status > 1
- Subjects who received prior systemic anti-cancer treatment in the metastatic setting
- Subjects without histologically documented Stage III or Stage IV melanoma, as per AJCC staging system
- Subjects with unknown BRAF V600 status (CRF)

<u>On-study:</u>

- Subjects receiving anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, standard or investigational agents for treatment of cancer) while on study therapy
- Subjects treated differently than as randomized (subjects who received the wrong treatment, excluding the never treated)

Listings will also be provided.

7.2.3 Unblinding

A summary of subjects whose treatment was unblinded during the course of the study will be provided based on a cumulative unblinding report prepared by a randomization coordinator within BMS. The frequency of subjects unblinded due to medical emergency or pregnancy versus those unblinded due to documented disease progression and decision to discontinue treatment will be reflected in this summary.

7.3 Study Population

Summaries of study population will be based on all randomized subjects, except that of subject disposition which will be based on all enrolled subjects.

7.3.1 Subject Disposition

The total number of subjects enrolled (randomized or not randomized) will be presented along with the reason for not being randomized. This analysis will be performed only on the all enrolled population only.

Number of subjects who discontinued study treatment along with corresponding reason will be tabulated by treatment group as treated. Reason for discontinuation will be derived from subject status CRF page. This analysis will be performed only on the all treated subjects population.

Number of subjects randomized but not treated along with the reason will be tabulated by treatment group as randomized. This analysis will be performed only on the all randomized population only.

A subject listing for all randomized subjects will be provided showing the subject's randomization date, first and last dosing date, off study date and reason for going off-study. A subject listing for subjects not randomized will also be provided, showing the subject's race, gender, age, consent date and reason for not being randomized.

7.3.2 Demographic and Baseline Characteristics

The following baseline characteristics will be summarized by treatment group, as randomized. All baseline presentations will identify subjects with missing measurements. Listings will also be provided.

- Age (descriptive statistics)
- Age category I (< 65, ≥ 65)
- Age category II (< 65, ≥ 65- < 75, ≥ 75)
- Gender (male, female)
- Race (white, black, asian, other)
- Region (US, EU, Australia, Rest of World)
- Baseline ECOG Performance Status (0, 1)
- M Stage at Study Entry (M0, M1a, M1b, M1c) (source: CRF)

- AJCC Stage at Study Entry (III, IV)
- Weight (descriptive statistics)
- PD-L1 Status (positive, negative/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant, wildtype) (source: CRF)
- BRAF mutation test (Cobas+THxID, Other, Unknown)
- Baseline LDH (≤ ULN, > ULN)
- Baseline LDH (≤ 2∗ULN, > 2*ULN)
- History of Brain Metastases (Yes, No)
- Smoking Status (Yes, No)
- Time from Initial Disease Diagnosis to Randomization (< 1 year,1-< 2 year, 2-< 3 year,3-< 4 year, 4-< 5 year, ≥ 5 year)
- All lesions (Investigator Tumor Assessments at Baseline): sites of disease, number of disease sites per subject.
- Target lesions (Investigator Tumor Assessments at Baseline): Presence of target lesions, site of target lesion, sum of longest diameter of target lesion.

Similarly the following IVRS data will be summarized by treatment group as randomized.

- BRAF mutation status (BRAF mutant/wildtype)
- M Stage at Study Entry (M0/M1a/M1b/M1c)
- PD-L1 Status (positive and negative/indeterminate)

7.3.3 Medical History

General medical history will be listed by subject.

7.3.4 Prior Therapy

The following will be summarized by treatment group as randomized.

- Prior neo-adjuvant therapy (yes/no)
- Prior adjuvant therapy (yes/no)
- Time from completion of prior adjuvant therapy to randomization (subjects who received prior adjuvant therapy), (< 6 months and > = 6 months)
- Prior surgery related to cancer (yes/no)
- Prior radiotherapy (yes/no)

Agents and medication will be reported using the generic name. A listing by subject will also be provided.

7.3.5 Baseline Examinations

Subjects with abnormal baseline physical exam results will be tabulated by examination criteria (eg, neck, cardiovascular, lungs, etc) and by treatment group as randomized.

7.3.6 Discrepancies between IVRS and CRF information

Summary tables (cross-tabulations) by treatment group as randomized for stratification factors will be provided to show any discrepancies between what was reported through IVRS vs. CRF data or clinical database (baseline).

- M Stage at Study Entry (IVRS vs. CRF data)
- PD-L1 status (IVRS vs. clinical database)
- BRAF Status (IVRS vs. CRF data)

7.4 Extent of Exposure

Analyses will be performed by treatment group "as treated" in all treated subjects, unless otherwise specified.

7.4.1 Administration of Study Therapy

The following parameters will be summarized (descriptive statistics) by treatment group:

- Time from randomization to first dose of study therapy (0 to 3 days, > 3 to 7, > 7 to 14, > 14 to 21, > 21 to 28, > 28)
- Number of concomitant doses received (nivolumab + ipilimumab-placebo, ipilimumab + nivolumab, and ipilimumab + nivolumab-placebo. A subject will be considered to have received concomitant doses of ipilimumab, and nivolumab or nivolumab-placebo, if both infusions are administered on the same date.

The following parameters will be summarized (descriptive statistics) by study therapy and treatment group:

- Number of doses received (nivolumab and ipilimumab):
- Cumulative dose (nivolumab and ipilimumab)
- Relative dose intensity (%) using the following categories: < 50%; 50 - < 70%; 70 - < 90%; 90 - < 110%; ≥ 110%. (nivolumab and ipilimumab)

Duration of treatment will be presented by treatment group using a Kaplan-Meier curve whereby the last dose date will be the event date for those subjects who are off study therapy. Median duration of treatment and associated 95% CI will be provided. Subjects who are still on study therapy will be censored on their last dose date.

A by-subject listing of dosing of study medication (record of study medication, infusion details, and dose changes) and a listing of batch numbers will be also provided.

Table 7.4.1-1: Study Therapy Parameter Definitions

	Nivolumab Arm A	Nivolumab Arm B	Ipilimumab Arms B and C
Dosing Schedule per Protocol	3 mg/kg every 2 weeks	1 mg/kg every 3 weeks for 4 doses followed by 3 mg/kg every 2 weeks	3 mg/kg every 3 weeks for 4 doses
Dose	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)	Dose (mg/kg) is defined as the minimum of [vial strength (mg/mL) *total volume infused (mL)] /most recent weight (kg) and nominal dose (mg/kg) * total volume infused (mL) /total volume prepared (mL)
Cumulative Dose	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.	Cum Dose (mg/kg) is the sum of the doses administered to a subject.
Dose Intensity (mg/kg/wk)	7x Cum dose/(Last dose date - Start dose date + 14)	For Combo phase (the first two cycles): 7x Cum dose in Combo phase /(Last dose date in Combo phase- Start dose date + 21) For Mono phase (cycle 3 and beyond): 7x Cum dose in Mono phase /(Last dose date - Start dose date in Mono phase + 14)	7 x Cum dose/(Last dose date - Start dose date + 21)
Relative Dose Intensity (%)	Cum dose/[3 x (Last dose date - Start dose date + 14)/14] x 100	Cum dose/[1 x (Last dose date - Start dose date + 21)/21] x 100, if the subject's last dose is in Combo phase Cum dose/[1 x 4 + 3 x (Last dose date - Start dose date - 84 + 14)/14] x 100 , if the subject's last dose is in Mono phase	Cum dose/[3 x (Last dose date - Start dose date + 21)/21] x 100
Duration of Treatment	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*	*Last dose date - Start dose date +1*

Volume infused, volume prepared, and weight are collected on the CRF. Nominal nivolumab dose collected in IVRS. i = 1, 2,...,N, where N = number of infusions. Cycle Duration (N) = 3 weeks for nominal 1 mg/kg nivolumab doses and 2 weeks for nominal 3 mg/kg. Intended dose per week is .33 mg/kg for nominal 1 mg/kg nivolumab doses and 1.5 mg/kg for nominal 3 mg/kg nivolumab doses.

7.4.2 Modifications of Study Therapy

7.4.2.1 Dose Delays

Each nivolumab and ipilimumab infusion may be delayed. A dose will be considered as actually delayed if the delay is exceeding 3 days (ie greater than or equal to 4 days from scheduled dosing date) for both nivolumab and ipilimumab. All studies drugs must be delayed until treatment can resume. Reason for dose delay will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of dose delays per subject, length of delay, and reason for delay

7.4.2.2 Infusion Interruptions and Rate Changes

Each nivolumab or ipilimumab infusion can be interrupted and/or the IV infusion rate can be reduced. This information will be retrieved from CRF dosing pages.

The following parameters will be summarized by treatment group:

- Number of subjects with at least one dose infusion interruption, the reason for interruption, and the number of infusion interruptions per subject.
- Number of subjects with at least one IV infusion rate reduction and the reason for reduction.

7.4.2.3 Dose Escalations

Dose escalations are not permitted for either nivolumab or ipilimumab.

7.4.2.4 Dose Reductions

Dose reductions are not permitted for either nivolumab or ipilimumab.

7.4.2.5 Dose Omissions

Dose omissions are not permitted for either nivolumab or ipilimumab.

7.4.3 Concomitant Medications

Concomitant medications, defined as medications other than study medications which are taken at any time on-treatment (ie, on or after the first day of study therapy and within 100 days following the last dose of study therapy), will be coded using the WHO Drug Dictionary.

The following summary table will be provided:

- Concomitant medications (subjects with any concomitant medication, subjects by medication class and generic term)

A by-subject listing will accompany the table.

7.5 Efficacy

7.5.1 Efficacy Analyses at Formal PFS Timepoint

7.5.1.1 PFS Primary Analysis

PFS analyses will be conducted using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in randomized subjects to compare each of the two experimental treatments to the control group. HRs and corresponding two-sided 99.5% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

Additionally, a descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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

PFS rates at 6, 12, and 18 months will be estimated using KM estimates on the PFS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated

The source of progression event (death versus progression) will be summarized by treatment group.

The status of subjects who are censored in the PFS KM analysis will be tabulated for each treatment group using the following categories:

- On-study (on-treatment, in follow-up)
- Off-study (lost to follow-up, withdrawn consent, never treated)
- Received subsequent anticancer therapy

7.5.1.2 PFS Sensitivity Analysis

Similar analyses of PFS will be performed using the following modifications.

- PFS using the strata as determined at baseline (CRF source for M-stage and BRAF status, clinical database for PD-L1) and the censoring scheme for primary analysis Table 4.1.1-1. This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.
- PFS accounting for tumor assessments occurring on or after initiation of anticancer therapy and censoring scheme 1 for sensitivity analysis (Table 7.5.1.2-1).
- PFS accounting for clinical progression, missing tumor assessments prior to PFS event (progression or death) and censoring scheme 2 for sensitivity analysis (Table 7.5.1.2-2).A subject is considered to have two or more missing tumor assessments if the elapsed time between the PFS event and the last assessment prior to the events is greater than 12 weeks + 10 days (94 days).

Table 7.5.1.2-1: Censoring Scheme 1 for Sensitivity Analysis of PFS

Situation	Date of Progression of Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 (excludes clinical progression)	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
Death without progression	Date of death	Progressed

Table 7.5.1.2-2: Censoring Scheme 2 for Sensitivity Analysis of PFS

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessment	Date of randomization	Censored
No on-study tumor assessments and no death	Date of randomization	Censored
Documented progression	Date of first documented progression per RECIST 1.1 or clinical progression	Progressed
No progression and no death	Date of last evaluable tumor assessment	Censored
New anticancer therapy, tumor-directed radiotherapy, or tumor-directed surgery received without progression reported prior or on the same day	Date of last evaluable tumor assessment prior to initiation of subsequent therapy	Censored
Death without progression	Date of death	Progressed
Death or progression after two or more missed visits	Date of last evaluable tumor assessment prior to the PFS event	Censored

Note: Censoring rule for death after two or missed visits supersedes rule for death without progression, where applicable

7.5.1.3 PFS Subgroup Analysis

To assess consistency of treatment effect in PFS in different subgroups, a 'forest' plot of the PFS unstratified hazard ratios and two-sided 95% CIs will be produced for the following variables:

- PD-L1 Status (positive and negative/indeterminate) (source: clinical database)
- BRAF mutation status (BRAF mutant and wildtype) (source: CRF)
- M Stage at Study Entry (M0/M1a/M1b and M1c) (source: CRF)

- Age category I (< 65 and ≥ 65)
- Age category II (< 65, ≥ 65- < 75, and ≥ 75)
- Gender (male and female)
- Race (white, black, asian, and other)
- Region (US, EU, Australia, and Rest of World)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes and No)
- Smoking Status (Yes and No)
- Baseline LDH (≤ ULN and > ULN)
- Baseline LDH (≤ 2∗ULN and > 2*ULN)
- AJCC Stage (III and IV)

If a subgroup category has less than 10 subjects per treatment group, HR will not be computed/displayed.

7.5.1.4 Analysis of ORR at PFS Timepoint

If PFS superiority is demonstrated for either experimental versus control comparison, a hierarchical testing approach for ORR will be applied (Section 7.5.4.1).

Primary Analysis

ORR analyses will be conducted using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) to compare each of the two experimental treatments to the control group. Associated odds ratios and 99.5% CIs will be calculated. An estimate of the difference in ORRs and corresponding 95% CI will be using calculated using CMH methodology and adjusted by the same stratification factors.

Additionally, a descriptive odds ratio and estimate of the difference in ORRs, along with corresponding two-sided 95% CIs, will be provided to evaluate differences between the two experimental arms.

ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms. BOR will be tabulated for each treatment group.

Sensitivity Analysis

Similar analyses of ORR will be performed using the following modification:

- ORR using the strata as determined at baseline (CRF source for M-stage and BRAF status, clinical database for PD-L1). This analysis will be performed only if the IVRS value for one stratification actor differs from the baseline value in at least 10% of randomized subjects.

Subgroup Analysis

To assess consistency of treatment effects in ORR in different subsets, a "forest" plot of the unweighted differences in ORRs and corresponding exact 95% CIs using the Newcombe method[13] will be produced for the same variables as in the PFS analysis (see Section 7.5.1.3). If a subgroup category has less than 10 subjects per treatment group, ORR will not be computed/displayed.

Duration of Objective Response

DOR curves in each treatment group will be estimated using the KM product-limit method for subjects with a BOR of CR or PR. Median DOR, corresponding two-sided 95% CI, and range will be reported.

Time to Objective Response

Summary statistics of TTR will be provided by treatment group for subjects with a BOR of CR or PR. TTR curves will be estimated using the KM product-limit method in all randomized subjects and will represent the cumulative rate of response over time. For non-responders, subjects will be censored at the maximum time of response + 1 day of all subjects in their respective treatment group. Cumulative response rates will be tabulated at Week 12, Month 6, and Month 12.

Other Analyses

The following subject-level graphics will be provided by treatment group, as randomized.

- For responders only, the time course of the following events of interest will be graphically displayed: tumor response, tumor progression, last dose received, and death.
- For response-evaluable subjects, a waterfall plot showing the best reduction in target lesion tumor burden based on investigator assessment.

7.5.1.5 Analysis of OS at PFS Timepoint

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

Descriptive HRs and corresponding two-sided 99.9% CIs for each of the experimental arms relative to the control group, and between experimental arms, will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source). There will be no formal comparison of OS at the PFS analysis timepoint.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up)
- off-study: (lost to follow-up, withdrew consent, etc)

7.5.2 Efficacy Analyses at Formal OS Timepoint

7.5.2.1 OS Primary Analysis

OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source) in all randomized subjects using Hochberg's procedure to address multiplicity (See Section 7.5.4). HRs and corresponding two-sided 98% CIs will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors.

Additionally, a descriptive HR and corresponding two-sided 95% CI will be provided to evaluate differences between the two experimental arms.

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

Survival rates at 6, 12, 18, 24, 36, 48 months, and then every year will be estimated using KM estimates on the OS curve for each treatment group. Minimum follow-up must be longer than the timepoint to generate the rate. Associated two-sided 95% CIs will be calculated.

The status of subjects who are censored in the OS KM analysis will be tabulated for each treatment group using following categories:

- on-study (on-treatment and not progressed, on-treatment progressed, in follow-up)
- off-study: (lost to follow-up, withdrew consent, etc)

To examine the assumption of proportional hazards in the Cox regression model, in addition to treatment, a time-dependent variable defined by treatment by time interaction will be added into the model. A two-sided Wald Chi-square p-value of less than 0.1 may indicate a potential nonconstant treatment effect.

7.5.2.2 OS Sensitivity Analysis

- OS for each of the two experimental arms will be compared to the control group using a two-sided unstratified log-rank test. Estimates of the HRs and corresponding two sided 98% CIs will be provided based on a Cox proportional hazards model, with treatment group as a single covariate.
- OS for each of the two experimental arms will be compared to the control group using a two-sided log-rank test stratified by PD-L1 status (clinical database source), BRAF status (CRF source), and M Stage at screening (CRF source) as determined at baseline. Estimates of the HRs and corresponding two-sided 98% CIs will be provided based on a Cox proportional hazards model, with treatment group as a single covariate, stratified by the above factors. This analysis will be performed only if at least one stratification variable at IVRS and at baseline disagrees for at least 10% of the randomized subjects.

7.5.2.3 OS Subgroup Analysis

To assess consistency of treatment effects in different subsets, a "forest" plot of the OS unstratified hazard ratios (and 95% CIs) will be produced for the same variables as in the PFS analysis (see Section 7.5.1.3). If a subgroup category has less than 10 subjects per treatment group, HR will not be computed/displayed.

7.5.2.4 OS Multivariate Analysis

A multivariate Cox model, stratified by PD-L1 status (clinical database source), BRAF status (CRF source), and M Stage at screening (CRF source) will be fitted to assess the treatment effect on OS when adjusted for potential prognostic factors. The following prognostic factors will be included in the model.

- Age category (< 65, ≥ 65- <75, ≥ 75)
- Gender (male and female)
- Baseline ECOG Performance Status (0 and 1)
- History of Brain Metastases (Yes, No)
- Baseline LDH (≤ ULN, > ULN)

HRs and corresponding 95% CIs will be provided for treatment variable and all covariates.

7.5.2.5 OS by Tumor Response

Exploratory analyses of survival by response category will be analyzed by treatment group using the landmark method[14]. Subjects still on study at the landmark time will be separated into two response categories according to whether they have responded before that time. This will assess whether survival from the landmark depends on the subject's response status at the landmark. Subjects who go off protocol (eg, subjects who die) before the time of landmark will be excluded from the analysis. Additional response categories could be also explored.

The survival curves from Week 12 and Month 6 by response status, for each treatment group will be produced using the KM product-limit method. Two sided, 95% CIs for median OS will be computed.

7.5.2.6 Updated Analysis of PFS at OS Timepoint

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

Descriptive HRs and corresponding two-sided 99.9% CIs for each of the experimental arms relative to the control group, and between experimental arms, will be estimated using a Cox proportional hazards model, with treatment group as a single covariate, stratified by PD-L1 status, BRAF status, and M Stage at screening (IVRS source). There will be no formal comparison of PFS at the OS analysis timepoint.

7.5.2.7 Updated Analysis of ORR at OS Timepoint

ORRs and corresponding 95% exact CIs will be calculated using the Clopper-Pearson method for each of the three treatment arms. BOR will be tabulated for each treatment group.

Associated odds ratios and 99.5% CIs for each of the experimental arms relative to the control group, and between experimental arms will be calculated. An estimate of the difference in ORRs and corresponding 95% CI will be using calculated using CMH methodology and adjusted by the same stratification factors.

DOR curves in each treatment group will be estimated using the KM product-limit method for subjects with a BOR of CR or PR. Median DOR, corresponding two-sided 95% CI, and range will be reported.

Summary statistics of TTR will be provided by treatment group for subjects with a BOR of CR or PR. TTR curves will be estimated using the KM product-limit method in all randomized subjects and will represent the cumulative rate of response over time. For non-responders, subjects will be censored at the maximum time of response + 1 day of all subjects in their respective treatment group. Cumulative response rates will be tabulated at Week 12, Month 6, and Month 12.

7.5.3 Efficacy Analyses at Both OS and PFS Timepoints

7.5.3.1 Subject Follow-Up

The extent of follow-up defined as the time between randomization date and last known date alive (for subjects who are alive) or death date (for subjects who died) will be summarized descriptively (median, min, max) for all randomized subjects.

The currentness of follow-up, defined as the time between last OS contact (ie, last known date alive or death date) and data cut-off date, will be summarized by treatment group. Subjects who died before data cut-off date will automatically have zero value for currentness of follow-up. For subjects with last known date alive after data cut-off date, they will have zero value for currentness of follow-up as well. The currentness of follow-up will be categorized into the following categories: 0 days, 1-30 days, 31-60 days, 61-90 days, 91-120 days, 121-150 days, 151 or more days.

7.5.3.2 Subsequent Therapy

Subsequent therapy and response to subsequent therapy will be summarized and listed.

- Subsequent Therapy
  - Chemotherapy by drug name
  - Hormonal or biologic therapy by drug name
  - Immunotherapy (anti-PD1 agents, anti-PDL1 agents, anti-CTLA4 agents, and others) by drug name
  - BRAF inhibitor by drug name

- MEK/NRAS inhibitor by drug name
- Other investigational agent by drug name
- Surgery
- Radiotherapy
- Any combination of the above

- By Subject Listing of Subsequent Therapy

7.5.4 Testing Hierarchy and Control of the Family-Wise Error Rate (FWER)

7.5.4.1 Progression Free Survival

An alpha of 0.005 (two-sided) will be allocated to each PFS comparison based on a Bonferroni adjustment to control the overall Type I error rate at 0.01 for PFS. If both PFS comparisons are significant, objective response rate (ORR) will tested for each comparison using Hochberg's procedure at alpha level = 0.01. If only one PFS comparison is significant, the corresponding ORR endpoint for that comparison will be tested at the alpha = 0.005 level. If no PFS comparisons are significant, ORR will not be tested.

7.5.4.2 Overall Survival

Hochberg's procedure will be applied to control the overall Type I error rate at 0.04 for OS.

7.5.5 Interim Analysis

Not applicable.

7.6 Safety

7.6.1 Deaths

See CORE Safety SAP[1].

7.6.2 Serious Adverse Events

See CORE Safety SAP[1].

7.6.3 Adverse Events Leading to Discontinuation of Study Therapy

See CORE Safety SAP[1].

7.6.4 Adverse Events Leading to Dose Modification

See CORE Safety SAP[1].

7.6.5 Adverse Events

See CORE Safety SAP[1].

7.6.6 Multiple Events

See CORE Safety SAP[1].

7.6.7 Select Adverse Events

See CORE Safety SAP[1].

7.6.8 Immune Modulating Medication

See CORE Safety SAP[1].

7.6.9 Clinical Laboratory Evaluations

7.6.9.1 Hematology

See CORE Safety SAP[1].

7.6.9.2 Serum Chemistry

Amylase and lipase will be summarized in addition to the serum chemistry parameters described in the CORE Safety SAP[1].

7.6.10 Vital Signs and Pulse Oximetry

See CORE Safety SAP[1].

7.6.11 Immunogenicity

Immunogenicity analyses will be performed separately for Nivolumab ADA Evaluable Subjects and Ipilimumab ADA Evaluable Subjects. Data listing will include all available ADA samples. However, subject-level ADA status will be defined by including only pre-infusion samples. See CORE Safety SAP[1].

7.6.12 Pregnancy

See CORE Safety SAP[1].

7.6.13 Clinical Safety Program

See CORE Safety SAP[1].

7.7 Pharmacokinetics

The concentration vs. time data obtained in this study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of nivolumab and to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Pharmacokinetic drug- drug interaction between nivolumab and ipilimumab will be studied by population PK approach. Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. The results of population PK, pharmacokinetic drug interaction and exposure response analyses will be reported separately.

7.8 Biomarkers

BRAF mutation status is embedded within the study design with analyses described in preceding sections. PD-L1 expression is being studied as a predictive biomarker in several other nivolumab melanoma studies including, but not limited to, CA209037 and CA209069.

7.8.1 PD-L1 Expression

Analyses of PD-L1 expression are descriptive in nature and intended to examine the distribution of PD-L1 expression and assess potential associations between PD-L1 expression and efficacy measures. If there is an indication of a meaningful association, future work will evaluate PD-L1 expression as a predictive biomarker, including selection of an optimal PD-L1 expression cut-off to classify subjects as PD-L1 positive or PD-L1 negative. Cut-off selection and validation will be conducted across studies and reported outside of individual clinical study reports. Additionally, PD-L1 analyses detailed below may be reported outside of the clinical study report in order to ensure the integrity of any potential validation analyses using data from this study.

PD-L1 status is a categorical variable by X% cut off for quantifiable PD-L1 expression:

- Positive: ≥ X% PD-L1 expression
- Negative: < X% PD-L1 expression

where X denotes the PD-L1 expression cut-off of 1%, 5% and 10%. Additional cut off values may also be explored.

PD-L1 expression quartile is a quartilized variable of quantifiable PD-L1 expression from the pooled population.

7.8.1.1 Analyses Methods

Analyses of PD-L1 will include:

- Examine the distribution of PD-L1 expression
- Assess potential association between PD-L1 expression quartile and PD-L1 status and efficacy measures
- Evaluate the potential predictive relationship of PD-L1 status and efficacy measures
- Test performance statistics such as sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)
- Assess potential association between PD-L1 expression quartile and PD-L1 status and overall AEs
- Concordance evaluation of PD-L1 status between verified assay and validated assay

7.8.1.2 Analyses at Formal PFS Timepoint

1) Descriptive statistics of PD-L1 expression and PD-L1 status, analyses will be based on all PD-L1 evaluable subjects if not otherwise specified

- Listing of all PD-L1 IHC data, all PD-L1 tested subjects
- Summary of tumor specimen acquisition and characteristics, all randomized subjects
- Summary statistics of PD-L1 expression by treatment groups of select subgroups, and overall.
- Box plot of PD-L1 expression by treatment group and overall
- Cumulative distribution plot of PD-L1 expression versus population percentile by treatment group and overall
- Waterfall plots of individual PD-L1 expression by treatment group

2) Frequency of PD-L1 expression quartile and Status (X%), including indeterminate and unknown if over 5% of subjects fall in this category, by treatment group for select subgroups and overall, all PD-L1 tested subjects. Selected subgroups are identical to the subgroups used for OS subgroup analysis. Evaluation of associations between PD-L1 expression quartile and PD-L1 status and efficacy measures. Analyses will be based all PD-L1 tested subjects if not otherwise specified. Each analysis will be performed for the subgroups listed below if not otherwise specified
    - Each PD-L1 expression quartile subgroup
    - Each PD-L1 status subgroup
    - PD-L1 unknown or indeterminate subgroup

<u>Analyses for ORR (BOR):</u>

- Box plots of PD-L1 expression versus Response Status by treatment group

For each of the subgroups:

- Frequency and percentage of investigator-assessed BOR will be summarized for each treatment group.
- Investigator-assessed ORR will be computed by treatment group along with exact 95% CIs using the Clopper-Pearson method.

<u>Analyses for PFS endpoint:</u>

For each of the subgroups:

- PFS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median PFS will be constructed based on a log-log transformed CI for the survivor function.
- Forest plot of Hazard Ratios with 95% CIs

3) Evaluation of the potential predictive relationship of PD-L1 status for efficacy measures, all PD-L1 evaluable subjects.

Analyses for ORR endpoint:

A logistic regression model will be fitted for response (yes=CR or PR, No=SD or PD or unknown) with treatment, PD-L1 status and the treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Odds ratio of treatment vs. control and its associated 95% CI will be reported for each of the PD-L1 status subgroup
- Odds ratio of PD-L1 positive vs. negative and its associated 95% CI will be reported for each treatment group

Analyses for PFS endpoint:

A Cox proportional hazards regression model will be fitted for PFS with treatment, PD-L1 status, and treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Hazard ratio of treatment vs. control and its associated 95% CI for each of the PD-L1 status subgroup
- Hazard ratio PD-L1 positive vs. negative and its associated 95% CI within each treatment group.

4) Test performance statistics for PD-L1 status vs. efficacy measures, all PD-L1 evaluable subjects
   - 2 by 2 contingency table of PD-L1 status by response status (yes=CR or PR; No=SD or PD or unknown) by treatment arm. Sensitivity, specificity, PPV and NPV will be reported along with the contingency table.

5) Association of all AE and PD-L1 expression, all treated, PD-L1 tested subjects

Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT by treatment group for following subgroups will be provided

- Each PD-L1 expression quartile subgroup
- Each PD-L1 status subgroup

6) PD-L1 unknown or indeterminate subgroup.Evaluation of concordance of PD-L1 status between verified assay and validated assay
    - Scatterplot of PD-L1 expression per validated Dako IHC assay versus PD-L1 expression per verified Dako IHC assay, all PD-L1 evaluable subjects
    - Contingency table of PD-L1 Status (5%) per verified Dako IHC assay (positive, negative, indeterminate based on clinical database) versus PD-L1 Status (5%) per validated Dako IHC assay (positive, negative, indeterminate), all randomized subjects
    - Contingency table of PD-L1 Status from IVRS (positive, negative/indeterminate) versus PD-L1 Status (5%) per validated Dako IHC assay (positive, negative/ indeterminate) all randomized subjects.

7.8.1.3 Analyses at Formal OS Timepoint

1) Evaluation of associations between PD-L1 expression quartile and PD-L1 status and efficacy measures. Analyses will be based all PD-L1 tested subjects if not otherwise specified. Each analysis will be performed for the subgroups listed below if not otherwise specified

- Each PD-L1 expression quartile subgroup
- Each PD-L1 status subgroup
- PD-L1 unknown or indeterminate subgroup

Analyses for OS endpoint:

For each of the subgroups:

- OS curves for each treatment group will be estimated using the Kaplan-Meier product limit method. Two-sided, 95% confidence intervals for median OS will be constructed based on a log-log transformed CI for the survivor function.

2) Forest plot of Hazard Ratios with 95% CIs Evaluation of the potential predictive relationship of PD-L1 status for efficacy measures, all PD-L1 evaluable subjects.

A Cox proportional hazards regression model will be fitted for OS with treatment, PD-L1 status, and treatment by PD-L1 status interaction. Although the study is not designed to have appropriate power to formally test the interaction of the model, an interaction test at significance level of 0.2 will warrant further exploration and the following statistics will be reported:

- Interaction p-value
- Hazard ratio of treatment vs. control and its associated 95% CI for each of the PD-L1 status subgroup
- Hazard ratio PD-L1 positive vs. negative and its associated 95% CI within each treatment group.

3) Association of all AE and PD-L1 expression, all treated, PD-L1 tested subjects

Overall summary of any AEs by worst CTC grade (any grade, grade 3-4, grade 5) presented by SOC/PT by treatment group for following subgroups will be provided

- Each PD-L1 expression quartile subgroup
- Each PD-L1 status subgroup
- PD-L1 unknown or indeterminate subgroup.

7.9 Outcomes research

Additional analysis of outcomes research endpoints, including EuroQoL EQ-5D and WPAI:GH, will be described in a separate analysis plan and presented outside of the clinical study report.

7.9.1 EORTC-QLQ-C30

Baseline measures will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale by treatment group, based on all randomized subjects with a baseline measurement.

Change from baseline will be summarized using descriptive statistics (N, mean, standard deviation, median, first and third quartiles, minimum, maximum) for each scale at each assessment time point by treatment group. This analysis will be performed in all randomized subjects who have an assessment at baseline and at least one on-study assessment.

EORTC-QLQ-C30 questionnaire completion rate, defined as the proportion of questionnaires actually received out of the expected number (ie, number of subjects on treatment or in follow up), will be calculated and summarized for each assessment time point by treatment group.

8 CONVENTIONS

The following conventions may be used for imputing partial dates for analyses requiring dates:

For missing and partial adverse event onset dates, imputation will be performed using the Adverse Event Domain Requirements Specification[15].

Missing and partial Non-Study Medication Domain dates will be imputed using the derivation algorithm described in 4.3.3 of BMS Non-Study Medication Domain Requirements Specification[16].

For death dates, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day. The imputed date will be compared to the last known date alive and the maximum will be considered as the death date.
- If the month or the year is missing, the death date will be imputed as the last known date alive
- If the date is completely missing but the reason for death is present the death date will be imputed as the last known date alive

For date of progression, the following conventions will be used for imputing partial dates:

- If only the day of the month is missing, the 1st of the month will be used to replace the missing day*.
- If the day and month are missing or a date is completely missing, it will be considered as missing.

*In cases where the date of death is present and complete, the imputed progression date will be compared to the date of death. The minimum of the imputed progression date and date of death will be considered as the date of progression.

For other partial/missing dates, the following conventions may be used:

- If only the day of the month is missing, the 15th of the month will be used to replace the missing day.
- If both the day and the month are missing, "July 1" will be used to replace the missing information.
- If a date is completely missing, it will be considered as missing.

The following conversion factors will be used to convert days to months or years: 1 month = 30.4375 days and 1 year = 365.25 days.

Duration (eg, time from first diagnosis to first dosing date, duration of response, and time to response) will be calculated as follows:

Duration = (Last date - first date + 1)

All statistical analyses will be carried out using SAS (Statistical Analysis System software, SAS Institute, North Carolina, USA) unless otherwise noted.

9 CONTENT OF REPORTS

All analyses described in this SAP will be included in the Clinical Study Report(s) except where otherwise noted. Refer to the Data Presentation Plan for mock-ups of all tables and listings.

10 REFERENCES

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Clinical Protocol CA209067

Amendment	Date of Issue	Summary of Major Changes
Statistical Analysis Plan v1.0	13-Dec-2013	Original Issue
Statistical Analysis Plan v2.0	11-Jul-2014	Statistical analysis plan updated to incorporate changes enacted with protocol amendment 06 to add progression free survival as a co-primary endpoint.
Statistical Analysis Plan v2.1	24-Oct-2014	Biomarker section updated with additional details on analyses of PD-L1 expression.
Statistical Analysis Plan v3.0	12-Feb-2015	• Immunogenicity section updated to align with Nivo program-level core immunogenicity SAP, including a clarification that only pre-infusion samples will be used to determine anti-drug antibody status, but all samples (both pre-infusion and end-of-infusion) will be included in the listings. • Slight modification to relative dose intensity derivation in Table 7.4.1-1 to align with project-level standards. • Other minor refinements to programming conventions to align with project-level standards.