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 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

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.
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BMS-936558 Nivolumab

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 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 (i.e., 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 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.
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

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 (±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.
- 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.
3.6 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.
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 Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

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

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

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

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

NOTE:

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

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

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 6.1.1 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.
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, hepatic, 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.\textsuperscript{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, i.e., 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