Clinical Protocol CA209066

A Phase 3, Randomized, Double-Blind Study of BMS-936558 (Nivolumab) vs Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

(CheckMate 066: CHECKpoint pathway and nivolumAb clinical Trial Evaluation 066)

Revised Protocol No.: 05
Incorporates Amendment(s): 09

Bristol-Myers Squibb Research and Development
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protocol may apply to partners to which BMS has transferred obligations, eg, a Contract Research Organization (CRO).

Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision, and archive the previous versions.
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<td>Revised Protocol 05</td>
<td>23-Sep-2016</td>
<td>Incorporates Amendment 09</td>
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<tr>
<td>Amendment 09</td>
<td>23-Sep-2016</td>
<td>Changes to the protocol:</td>
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<tr>
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<td>- Section 1.4.4.3 Rationale for Flat Dose 480 mg nivolumab every 4 Weeks is added</td>
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<td>- Section 1.4.4.4 Rationale for Shorter Infusion Time for Nivolumab is added</td>
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<td>- Section 3.1 Study Design and Duration is changed to add a new study schematic and</td>
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<td>optional nivolumab 480 mg flat dose every 4 weeks.</td>
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<td>It addition, it removes PK assessment for subjects on nivolumab weight-based dosing</td>
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<td>including treatment and follow up phases, while requires for subjects on nivolumab</td>
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<td>flat dosing as specified in section 5.5. It adds extended Tumor Assessments frequency</td>
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<td>to every 24 weeks for treatment responders, and PRO instruments frequency to every 6 months in follow up phase.</td>
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<td>- Section 3.3.1 Inclusion Criteria, 3.b) is changed to require that contraception in</td>
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<td>women continue for 5 months</td>
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<td>- Section 3.3.1 Inclusion Criteria, 3.e) is changed to require that contraception in</td>
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<td>men continue for 7 months</td>
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<td>- Section 4.1.3 Handling and Dispensing is changed to specify a requirement to start</td>
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<td>nivolumab flat dosing 2 weeks after the last dose of weight based nivolumab. In</td>
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<td>addition, it specifies infusion time of 30 minutes for nivolumab 3mg/kg every 2</td>
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<td>weeks and nivolumab Flat Dose 480 mg every 4 Weeks.</td>
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<td>- Section 4.2 Method of Assigning Subject Identification is changed to add requirement of IVRS</td>
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<td>- Section 4.3 Selection and Timing of Dose for Each Subject is changed, concerning</td>
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<td>subjects on nivolumab flat dosing, to clarify that a treatment cycle is 4 weeks,</td>
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<td>subjects may be dosed no less than 26 days from the previous dose, and up to 3</td>
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<td>working days after the scheduled date</td>
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<td>- Table 4.3-2 Study Dosing Schedule is changed its title from Blinded Study Dosing</td>
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<td>Schedule. It is also changed to include schedule of nivolumab 480mg flat dosing.</td>
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<td>- Section 4.3.2 Dose Delay Criteria is changed to require that if administration of</td>
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<td>nivolumab flat dose is delayed more than 3 business days, the dose should be</td>
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<td>completely skipped.</td>
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<td>- Section 4.3.4 Criteria to Resume Treatment is changed to specify subjects receiving</td>
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<td>nivolumab flat dosing at 480mg every 4 weeks who meet criteria for discontinuation</td>
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<td>may resume weight based dosing at 3mg/kg every 2 weeks when the drug related AE(s)</td>
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|                        |               |   resolve(s) to Grade ≤ 1 or baseline, after discussion and approval by the BMS Medical Monitor/designee. It also adds that subjects receiving nivolumab flat dosing if dosing is delayed > 10 weeks from the scheduled dosing, the subject must be permanently discontinued from study therapy, expect as specified in Section 6.0.
4.3.5.

- Section 4.3.5 Discontinuation Criteria is changed to add that subjects receiving nivolumab flat dosing should be permanently discontinued study therapy if dosing is delayed > 10 weeks from the scheduled dosing except for dosing interruption to allow prolonged steroid tapers to manage drug-related adverse events or non-drug related reasons. Both cases need BMS Medical Monitor’s consultation and approval beforehand.

- Table 5.1.2-2: Open-label Procedural Outline (CA209066) Nivolumab 3mg/kg every 2 weeks Arm is changed to remove CBC assessment from Day 15 and 29, and PK/immunogenicity assessment from from Day 15. It changes Laboratory Tests assessment frequency to every month, and extends Tumor Assessments frequency to every 24 weeks for treatment responders.

- Table 5.1.2-3: Open-label Procedural Outline (CA209066) Nivolumab 480 mg every 4 weeks Arm is added to clarify required procedures for nivolumab 480 mg every 4 weeks

- Table 5.1.2-4: Open-label Procedural Outline (CA209066) Dacarbazine Arm is changed to extend Tumor Assessments frequency to 24 weeks for treatment responders.

- Table 5.1.2-5: Open-Label Follow-Up Assessments (CA209066) for All Subjects except for subjects previously randomized to Dacarbazine and entering Nivolumab Open-Label Phase is renamed from Open-Label Follow-Up Assessments (CA209066). It is changed to extend EQ-5D assessment frequency to every 6 months, add clarification in frequency of Tumor Assessments, and remove requirements in Immunogenicity/PK assessment.

- Table 5.1.2-6 Open-Label Follow-Up Assessments (CA209066) for Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase (Nivolumab Open-Label Extension Phase) is changed to add clarification in frequency of Tumor Assessments and remove requirements in Immunogenicity/PK assessment.

- Section 5.3 Safety Assessments is changed to add required lab analysis for subjects on nivolumab 480 mg every 4 weeks. Also, for subjects on nivolumab 3mg/kg every 2 weeks, it removes CBC assessment from Day 15 and 29, and changes Laboratory Tests assessment frequency to every month.

- Section 5.4 Efficacy Assessments is changed to allow extension in tumor assessment frequency up to 24 weeks for treatment responders

- Section 5.5 Pharmacokinetic/Immunogenicity Assessments is changed to clarify sampling schedule of nivolumab 480 mg flat dose every 4 weeks.

- Table 5.5-1 Sampling Schedule for BMS-936558 (Nivolumab) or Matched Placebo is changed to remove PK sampling for subjects receiving nivolumab 3 mg/kg every 2 weeks in follow up phase.

- Table 5.5-2 Sampling Schedule for BMS-936558 (Nivolumab)
Clinical Protocol CA209066
BMS-936558 nivolumab

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<td>Amendment 08</td>
<td>06-May-2015</td>
<td>Changes to the Protocol:</td>
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<td>1. Section 3.1, Study Design and Duration, Follow-up Phase,</td>
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<td>a) Added new paragraph after the last bullet.</td>
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<td>Overall survival is a key endpoint of this study. Post study follow-up is of</td>
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<td>critical importance and is essential to preserving subject safety and the</td>
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<td>integrity of the study. Subjects who discontinue study drug must continue to</td>
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<td>be followed for collection of outcome and/or survival follow-up data as</td>
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<td>required and in line with section 3.1 until death or the conclusion of the study.</td>
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<td>BMS may request that survival data be collected on all randomized subjects</td>
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<td>outside of the protocol defined window as detailed in the Time and Events Table</td>
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<td>5.1.2-4 Follow-up Assessments (CA209066)  ) and Table 5.1.2-5. At the time of</td>
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<td>this request, each subject will be contacted to determine their survival status</td>
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<td>unless the subject has withdrawn consent for all contact.</td>
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<td>2. Section 5.1, Table 5.1.2-4: Follow-Up Assessments (CA209066) added the</td>
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<td>following sentence to footnote b: BMS may request that survival data be</td>
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<td>collected on all randomized subjects outside of the protocol defined window.</td>
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<td>3. Section 5.1, Table 5.1.2-5: Open-Label Follow-Up Assessments (CA209066) for</td>
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<td>Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase</td>
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<td>(Nivolumab Open-Label Extension Phase) added the following sentence to footnote</td>
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<td>b: BMS may request that survival data be collected on all randomized subjects</td>
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<td>outside of the protocol defined window.</td>
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Administrative Letter 01 | 04-Dec-2014 | Corrects typographical errors and unclarities pertaining to Revised Protocol 03, dated 09-Jul-2014 |
Revised Protocol 03       | 09-Jul-2014  | Incorporates Amendment(s): 07                                                      |
Amendment 07              | 09-Jul-2014  | This amendment provides modifications to the protocol based on recommendations of the study’s Data Monitoring Committee (DMC). |
|                   |               | 1. According to the DMC, the most current data showed clear                        |
evidence of a survival benefit in subjects receiving nivolumab compared to dacarbazine. As a result of these recommendations, this protocol amendment is implemented to provide a mechanism for subjects in the follow-up phase of the study who have received and discontinued from dacarbazine to receive nivolumab, as well as to provide a mechanism for subjects who are currently receiving dacarbazine to receive nivolumab upon discontinuation of dacarbazine.

2. Prior to implementation of this amendment, all subjects were unblinded. As a result of this unblinding, this amendment also removes the administration of placebo infusions and study activities and procedures associated with placebo infusions.

3. This amendment applies to all subjects.

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<td>Amendment 06</td>
<td>08-May-2013</td>
<td>Removes the specified timeframe around the timing of tumor tissue collection for inclusion.</td>
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<td>Inclusion of recommendations for adverse events management in subjects requiring treatment with high dose steroids or other immunosuppressive agents.</td>
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<td>Expanded allowance for palliative therapy at time of treatment beyond progression.</td>
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<td>Incorporate other minor changes to correct and/or clarify protocol requirements and procedures</td>
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<tr>
<td>Revised Protocol 01</td>
<td>07-Mar-2013</td>
<td>Incorporates Amendment(s): 03</td>
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<tr>
<td>Amendment 03</td>
<td>07-Mar-2013</td>
<td>Inclusion of non-clinical safety findings related to reproductive toxicology data.</td>
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<tr>
<td>Original Protocol</td>
<td>20-Sep-2012</td>
<td>Not applicable</td>
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SYNOPSIS

Clinical Protocol CA209066

(CheckMate 066: CHECKpoint pathway and nivolumAb clinical Trial Evaluation 066)

Protocol Title: A Phase 3, Randomized, Double-Blind Study of BMS-936558 (Nivolumab) vs Dacarbazine in Subjects with Previously Untreated, Unresectable or Metastatic Melanoma

Investigational Product(s), Dose and Mode of Administration, Duration of Treatment with Investigational Product(s):
BMS-936558 (Nivolumab) dosed intravenously over 30 minutes at 480 mg flat dose every 4 weeks, 3 mg/kg every 2 weeks or dacarbazine dosed intravenously over 60 minutes at 1000 mg/m$^2$ every 3 weeks

Study Phase: 3

Research Hypothesis:
Treatment with BMS-936558 (Nivolumab) will improve overall survival (OS) when compared to dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.

Objectives:

Primary Objective: To compare the clinical benefit, as measured by the duration of OS, provided by BMS-936558 (Nivolumab) vs. dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.

Secondary Objectives:
1. To compare the duration of investigator-assessed progression-free survival (PFS) of BMS-936558 (Nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.
2. To compare the investigator-assessed objective response rate (ORR) of BMS-936558 (Nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.
3. To evaluate whether PD-L1 expression is a predictive biomarker for OS
4. To evaluate the Health Related Quality of Life (HRQoL) as assessed by 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 BMS-936558 (Nivolumab) plus placebo vs. dacarbazine plus placebo in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must be known BRAF wild-type. Tumor tissue from an unresectable or metastatic site must be analyzed and evaluable for PD-L1 status during the screening period in order to be randomized.

Subjects will be randomized 1:1 and stratified by PD-L1 status (positive vs. negative/indeterminate) and M stage (M0/M1a/M1b vs. M1c). Subjects will be treated with BMS-936558 (Nivolumab) 3 mg/kg IV every 2 weeks plus placebo IV every 3 weeks or dacarbazine using the standard dose and schedule (1000 mg/m$^2$ IV every 3 weeks) plus placebo IV every 2 weeks.

Each cycle will be approximately 6 weeks in duration (3 doses of BMS-936558 (Nivolumab) or BMS-936558 (Nivolumab)-matched placebo and 2 doses of dacarbazine or dacarbazine-matched placebo per cycle).
Clinical Protocol
BMS-936558
nivolumab

Figure 1: Study Schematic

Unresectable or metastatic melanoma:
- Previously untreated
- BRAF wild-type
- Tissue available for PD-L1 testing

Stratify by:
- PD-L1 status: Positive vs. Negative/Intermediate
- M stage: M0/M1a/M1b vs. M1c

BMS-936558
3 mg/kg IV every 2 weeks + Placebo IV every 3 weeks*

Dacarbazine
1000 mg/m² IV every 3 weeks + Placebo IV every 2 weeks*

Treat until progression** or unacceptable toxicity
1° Endpoint: OS

* Subjects who receive BMS-936558 will also receive a dacarbazine-matched placebo, while subjects who receive dacarbazine will also receive a BMS-936558-matched placebo.
** Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

Amendment 07 Update: All subjects were unblinded based on the recommendation of the DMC. With this amendment, all subjects randomized to the dacarbazine arm who qualify for nivolumab therapy may enter the Nivolumab Open-Label Extension Phase.

Amendment 09 Update:

Figure 2 Study Schematic

Double blind phase

Randomization 1:1
Unresectable or metastatic melanoma: previously untreated

Nivolumab 3 mg/kg IV every 2 weeks + Placebo IV every 3 weeks

Dacarbazine 1000 mg/m² every 3 weeks + Placebo IV every 2 weeks

Nivolumab 480 mg IV every 4 weeks*

Open label treatment phase

Nivolumab 3 mg/kg IV every 2 weeks

Dacarbazine 1000 mg/m² every 3 weeks

Nivolumab 480 mg IV every 4 weeks*

Nivolumab 480 mg IV every 4 weeks*

Nivolumab 480 mg IV every 4 weeks*

* Switch to Nivolumab 480 mg IV every 4 weeks is optional.

All subjects currently receiving nivolumab or eligible to receive nivolumab 3 mg/kg dosing will have the option to switch to nivolumab 480 mg flat dose every 4 weeks, Switch to flat dose is optional.

Study Population:

Key Inclusion Criteria:
- Men and women ≥ 18 years of age.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

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Approved v6.0 930063436 8.0
• Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system. 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 as per RECIST 1.1.

• 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.

• Known BRAF wild-type as per regionally acceptable V600 mutational status testing. BRAF mutant subjects and those with indeterminate or unknown BRAF status are not permitted to randomize.

**Key Exclusion Criteria:**

• Active brain metastases or leptomeningeal metastases.

• 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 therapy, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

Subjects must also meet other study criteria including exclusions for medical history, positive Hep B/C, HIV, and pregnancy tests, and other laboratory criteria.

**Amendment 07 Update:** Specific eligibility criteria for subjects randomized to the dacarbazine arm and now entering the Nivolumab Open-Label Extension Phase are included in the protocol body.

**Study Assessments:**

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 metastic site must be available and sent to a central laboratory for biomarker analyses. PD-L1 status must be determined prior to randomization and will be used as a stratification factor. PD-L1 status must be classified as positive, negative, or indeterminate in order to be randomized. If an insufficient amount of recently acquired tissue from a unresectable or metastatic site is available prior to the start of the screening phase, subjects must consent to allow the acquisition of fresh tumor tissue by study personnel for performance of biomarker analyses.

**Amendment 07 Update:** Details of the open-label phase are included in the protocol body and Table 5.1.2-1.

**Treatment Phase:**

• Begins with the randomization call to the IVRS. The subject is randomly assigned to either the BMS-936558 (Nivolumab) + placebo arm (Arm A) or the dacarbazine + placebo arm (Arm B).

• PRO instruments must be completed after randomization, prior to the first dose of study therapy according to the schedule in Table 5.1.1-2.

• On-study labs (Cycle 2 and beyond) should be drawn within 72 hours prior to dosing.

• Within 3 days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1).

• Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test during Week 1 and Week 4 of each cycle following Day 1 of treatment. A pregnancy test should be documented within 24 hours prior to the start of investigational product.
PK samples and immunogenicity samples will be completed according to the schedule in Table 5.5-1.

Subjects on the BMS-936558 (Nivolumab) + placebo arm (Arm A) are dosed with BMS-936558 (Nivolumab) every 2 weeks and placebo every 3 weeks (Table 5.1.1-2) with allowances for delay up to a maximum of 6 weeks from last dose (see Section 4.3.4). Subjects on the dacarbazine + placebo arm (Arm B) are dosed with dacarbazine every 3 weeks and placebo every 2 weeks (Table 5.1.1-2) with allowances for delay up to a maximum of 6 weeks from last dose (see Section 4.3.7).

Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 9 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.

Amendment 09 Update: Details of the open-label phase are included in the protocol body and Tables 5.1.2-2, 5.1.2-3, and 5.1.2-4.

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 (referred to as X visits in Table 5.1.1-3) include collection of PK/immunogenicity samples
- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 9 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 or discontinuation of treatment, whichever occurs later.
- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after last dose.
- After completion of the two X follow-up visits, subjects will be followed every 3 months for survival.
- PRO instruments will be completed according to the schedule in Table 5.1.1-3.

Amendment 09 Update: Details of the open-label phase are included in the protocol body and Tables 5.1.2-5 and 5.1.2-6.

Statistical Considerations:

Sample Size: The sample size is calculated in order to compare OS between subjects randomized to receive BMS-936558 (Nivolumab) vs dacarbazine. Approximately 410 subjects will be randomized to the two treatment arms in a 1:1 ratio.

The study requires at least 312 deaths, with an interim analysis after 218 deaths (70% of total deaths needed for final analysis) to ensure approximately 90% power to detect a hazard ratio (HR) of 0.69 with an overall type I error of 0.05 (two-sided). The HR of 0.69 corresponds to a 45% increase in the median OS, assuming a median OS of 10 months for dacarbazine and 14.49 months for BMS-936558 (Nivolumab). The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O’Brien-Fleming boundaries.

Amendment 07 Update: The timing of the final analysis of OS will be revised based on the early stopping of the blinded portion of the study and initiation of the open-label phase.

Endpoints:

Primary Endpoint:

OS in all randomized subjects is the primary endpoint for this study.
Secondary Endpoints:

If OS superiority in all randomized subjects is demonstrated, a gatekeeping testing approach for key secondary endpoints will be applied. Key secondary endpoints include PFS in all randomized subjects and ORR in all randomized subjects.

Analyses:

The primary analysis of OS in all randomized subjects will be conducted using a two-sided log-rank test stratified by PD-L1 status and M stage. The hazard ratio and corresponding two-sided (1-adjusted \( \alpha \))% confidence interval (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs and OS rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.
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1 INTRODUCTION AND STUDY RATIONALE

1.1 Study Rationale

CA209066 (CheckMate 066: CHECKpoint pathway and nivoluMAb clinical Trial Evaluation 066) is a Phase 3, randomized, double-blind study of BMS-936558 (Nivolumab) plus placebo versus dacarbazine plus placebo in subjects with previously untreated, unresectable or metastatic melanoma. This study will allow for direct comparison of the clinical benefit, as measured by overall survival, provided by BMS-936558 (Nivolumab) vs dacarbazine. If the safety profile is acceptable and BMS-936558 (Nivolumab) is shown to improve OS, this study would support the approval of BMS-936558 (Nivolumab) in subjects with previously untreated, unresectable or metastatic melanoma.

Amendment 07 Update:

The Data Monitoring Committee (DMC) for the CA209066 study convened on 10-Jun-2014. According to the DMC, the most current data showed clear evidence of a survival benefit in subjects receiving nivolumab compared to dacarbazine. As a result, the DMC made the following recommendations:

1. The nivolumab treated subjects should continue to be treated and monitored as specified in the protocol.
2. The subjects still being treated with dacarbazine should continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from dacarbazine in the judgment of the investigator.
3. The subjects randomized to dacarbazine who have ended study treatment should be allowed to crossover to receive treatment with nivolumab.

As a result of these recommendations, all study subjects were unblinded.

The revised protocol (that includes Amendment 07) allows subjects who have received and discontinued from dacarbazine to receive nivolumab. Also, subjects who are currently receiving dacarbazine can receive nivolumab upon discontinuation of dacarbazine.

In order to receive subsequent therapy with nivolumab, all subjects who received prior dacarbazine and qualify for subsequent treatment with nivolumab, must sign an informed consent and will enter the Nivolumab Open-Label Extension phase of the study.

1.2 Research Hypothesis

Treatment with BMS-936558 (Nivolumab) will improve OS when compared to dacarbazine in subjects with previously untreated, unresectable or metastatic positive melanoma.
1.3 **Objectives**

1.3.1 **Primary Objectives**

To compare the clinical benefit, as measured by the duration of OS, provided by BMS-936558 (Nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.

1.3.2 **Secondary Objectives**

- To compare the duration of investigator-assessed progression-free survival (PFS) of BMS-936558 (Nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.
- To compare the investigator-assessed objective response rate (ORR) of BMS-936558 (Nivolumab) vs dacarbazine in subjects with previously untreated, unresectable or metastatic melanoma.
- To evaluate whether PD-L1 expression is a predictive biomarker for OS.
- To evaluate the Health Related Quality of Life (HRQoL) as assessed by European Organisation for Research and Treatment of Care (EORTC) QLQ-C30.

1.3.3 **Exploratory Objectives**

- To evaluate duration of and time to objective response of BMS-936558 (Nivolumab) and dacarbazine.
- To assess the overall safety and tolerability of BMS-936558 (Nivolumab) vs dacarbazine.
- To characterize pharmacokinetics of BMS-936558 (Nivolumab) and explore exposure-response (exposure-safety and exposure-efficacy) relationships with respect to selected safety and efficacy endpoints.
- To characterize the immunogenicity of BMS-936558 (Nivolumab).
- To explore potential biomarkers associated with clinical response to BMS-936558 (Nivolumab) by analyzing tumor tissue specimens, serum and peripheral blood for markers including, but not limited to, PD-1, PD-L1 and PD-L2, and lymphocytic cell populations involved in regulating immune responses 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 occurrence 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 assess changes in health status in treatment groups by the EuroQoL EQ-5D both on treatment and during the survival follow-up period.
1.4 Product Development Background

1.4.1 BMS-936558 (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 costimulatory 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 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 positive tumors as well as in tumors that are negative for the expression of PD-L1.\textsuperscript{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.\textsuperscript{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.\textsuperscript{7} Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.\textsuperscript{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.\textsuperscript{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.\textsuperscript{27}

BMS-936558 (Nivolumab) is a fully human, IgG4 (kappa) isotype, mAb that binds PD-1. Blockade of the PD-1 pathway by BMS-936558 (Nivolumab) was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-$\gamma$ release in the MLR.\textsuperscript{28} The effect of BMS-936558 (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 BMS-936558 (Nivolumab), versus an isotype-matched control antibody, augmented IFN-$\gamma$ secretion from CMV-specific memory T-cells in a dose-dependent manner. PD-1 blockade by BMS-936558 (Nivolumab) is therefore considered a promising immunotherapeutic option.

1.4.2 Melanoma: Background and Standard Treatments

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.\textsuperscript{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. The five-year survival rate is 15% for late-stage disease.

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

In the Phase 3 study MDX010-20, ipilimumab monotherapy demonstrated a hazard ratio (HR) of 0.66 and a 4-month median OS benefit compared to gp100 in pretreated advanced melanoma subjects. 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 advanced melanoma based on data from MDX010-20 and without restriction to line of therapy, in part because of the results of an additional Phase 3 randomized ipilimumab clinical study, CA184024. 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 to monotherapy dacarbazine. In the EU, 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 V600E mutation positive. Vemurafenib is approved in the US and in the EU for the treatment of BRAF V600E mutation-positive advanced melanoma subjects regardless of line of therapy. 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. 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%).

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. 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%).

Patients should preferentially be treated within clinical trials. However, not all advanced melanoma patients have access to clinical trials. In these cases, therapy for advanced disease with several metastases in different anatomical regions may initially use well-tolerated cytostatics such as dacarbazine, taxanes, fotemustine or others, cytokines...
(Interferons, Interleukin-2 [IL-2]), or combinations. There is no standard therapy. However, in this situation, dacarbazine is at least considered as a reference drug.\textsuperscript{39}

### 1.4.3 Summary of Results from the BMS-936558 (Nivolumab) Program

#### 1.4.3.1 Summary of Safety

Two studies have contributed to most of the monotherapy clinical experience with BMS-936558 (Nivolumab) in subjects with melanoma and other solid malignancies. CA209001 was a Phase 1 single-dose dose escalation study in 39 subjects with previously treated advanced or metastatic cancer. Subjects received a single dose of BMS-936558 (Nivolumab) at 0.3, 1, 3, or 10 mg/kg with an option for re-treatment at 3 months. CA209003 is an ongoing Phase 1 open-label, multiple dose escalation study in 304 subjects with select previously treated advanced solid tumors, including melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and hormone-refractory prostate cancer. Subjects received BMS-936558 (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 BMS-936558 (Nivolumab) in the dose range of 0.1-10 mg/kg.

At least one AE, regardless of causality, was reported for all 39 subjects (100\%) treated in CA209001 with the majority of subjects experiencing at least 1 AE of \( \geq \) Grade 3. The most frequently reported AEs, regardless of causality, included fatigue (56.4\%), nausea (43.6\%), proteinuria (38.5\%), constipation (33.3\%), back pain (33.3\%), dry mouth (28.2\%), vomiting (28.2\%), rash (25.6\%), and dyspnea (25.6\%). There was no dose-related pattern with regard to the incidence, severity or relationship of AEs. The most common laboratory abnormality (reported in \( \geq 10\% \) of subjects) that was considered related to BMS-936558 (Nivolumab) and of \( \geq \) Grade 3 severity was decreased CD4 lymphocyte count (7 subjects, 17.9\%). There were 68 SAEs (Grades 1-4) reported in 23 of the 39 (59\%) treated subjects in CA209001. Of these, 2 subjects each reported treatment-related SAEs of hypothyroidism (Grade 2), colitis (Grade 3), and anemia (Grade 2). Two subjects discontinued study drug due to AEs; 1 subject due to Grade 2 polymyalgia rheumatica, which was considered possibly related to study drug, and the other subject due to complications from progressing central nervous system metastases, which were considered unrelated to study drug. Twelve (12) deaths were reported during the course of the study or within 30 days of last dose of study drug, all considered unrelated to BMS-936558 (Nivolumab).

No maximal tolerated dose was identified in the CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. BMS-936558 (Nivolumab) related AEs of any grade occurred in 72.4\% of subjects. The most frequent drug-related AEs occurring in \( \geq 5\% \) of subjects included: fatigue (25.7\%), rash (13.5\%), diarrhea (11.8\%), pruritus (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 \( \geq 1\% \) of subjects were: fatigue (1.6\%), lymphopenia (1.3\%), abdominal pain (1\%), diarrhea (1\%).
(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. Because of the potential for clinically meaningful BMS-936558 (Nivolumab)-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected pulmonary toxicity, diarrhea or suspected colitis, hepatotoxicity, endocrinopathy and nephrotoxicity. These algorithms are updated regularly and are therefore included as an appendix within the most recent version of the BMS-936558 (Nivolumab) IB.

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.

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

Preliminary new non-clinical safety findings of adverse pregnancy outcomes and infant losses in the absence of overt maternal toxicity have been reported. The findings of increased late stage pregnancy loss and early infant deaths/euthanasia in BMS-936558 (Nivolumab) exposed pregnant monkeys suggest a potential risk to human pregnancy if there is continued treatment with BMS-936558 (Nivolumab) during pregnancy.

As of 03-Apr-2013, three subjects out of approximately 1,200 patients on BMS-936558 (Nivolumab) (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 BMS-936558 (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 corticosteroid 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 events:
• Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as *Pneumocystis jiroveci*, bacterial 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 profile of BMS-936558 (Nivolumab), including results from other clinical studies, are available in the IB.

### 1.4.3.2 Summary of Clinical Activity

In CA209001 and CA209003, the clinical activity of BMS-936558 (Nivolumab) was demonstrated in a variety of tumor types, including melanoma, RCC, NSCLC, and CRC. 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) and across dosing schedules (every 2 weeks dosing for CA209003, single administration with possibility of retreatment at 3 months in CA209001).

In CA209001, all treated subjects (n = 39) were evaluable for tumor response. Partial response (PR) was reported in 3 subjects and stable disease (SD) was reported in 10 subjects. Subjects with PRs included 1 subject with CRC treated at 3 mg/kg and 1 subject each with melanoma and RCC, both treated at 10 mg/kg. Tumor responses were maintained in these subjects as of their last radiological tumor assessments at 26, 3, and 18 months, respectively as of the clinical data cut-off date. The subject with RCC had received multiple prior therapies, including sunitinib and sorafenib. In 2 of the 10 subjects with SD, stable disease was maintained for more than 6 months.

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 BMS-936558 (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 rate was 41%, 33%, 48%, 55%, and 30% in melanoma subjects treated at 0.1, 0.3, 1, 3, and 10 mg/kg, respectively.
1.4.3.3 **Clinical Pharmacology Summary**

Single-dose pharmacokinetics (PK) of BMS-936558 (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 BMS-936558 (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 BMS-936558 (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 BMS-936558 (Nivolumab) is 17 to 25 days, which is consistent with half life of endogenous IgG4, indicating that the elimination mechanism of BMS-936558 (Nivolumab) may be similar to IgG4. Both elimination and distribution of BMS-936558 (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 BMS-936558 (Nivolumab).

1.4.4 **Rationale for CA209066 Study Design**

1.4.4.1 **Rationale for Choice of Comparator**

According to the most recent European Society for Medical Oncology (ESMO) clinical practice guidelines for melanoma, dacarbazine should be considered a reference drug for metastatic melanoma. Subsequent to the publication of these recent guidelines, 2 agents have been approved by the European Commission for metastatic melanoma: ipilimumab (indicated in previously treated patients) and vemurafenib (indicated in patients who harbor the BRAF V600E mutation). Given that the patient population for the proposed Phase 3 study CA209066 includes treatment-naïve subjects who have BRAF wild-type status, dacarbazine is an appropriate comparator for this registrational trial.

1.4.4.2 **Rationale for Dose and Schedule of BMS-936558 (Nivolumab)**

The dose and schedule of BMS-936558 (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 (database lock: 24-Feb-2012; dosing data cut off for efficacy: first dose by 01-Jul-2011). 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 antitumor activity of BMS-936558 (Nivolumab) tended to increase with dose, as did the...
incidence of SAEs. The anti-tumor activity of BMS-936558 (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.

BMS-936558 (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 BMS-936558 (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 maximize the benefit-risk ratio.

1.4.4.3 Rationale for Flat Dose 480 mg nivolumab every 4 Weeks

Nivolumab monotherapy has been extensively studied in a number of tumor types including Melanoma (MEL), Non-Small Cell Lung Cancer (NSCLC), Renal Cell Carcinoma (RCC), chHL, Head & Neck (H&N) and Urothelial Carcinoma (UC) with body weight normalized dosing (mg/kg). Nivolumab Pharmacokinetics were determined to be linear, with dose proportional exposures over a dose range of 0.1 mg/kg to 10 mg/kg. Nivolumab clearance and volume of distribution were found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. A flat dose is expected to reduce prescription dosing errors, shorten pharmacy preparation time, and improve ease of administration. Extending the dosing interval to 4 weeks provides benefit to patients as they would have increased time between clinical visits, as compared to Q2W dosing schedule.

A flat dose of 480 mg every 4 weeks was selected based on equivalence to the approved 3 mg/kg every 2 weeks at the median body weight of ~80 kg in nivolumab treated subjects. A PPK model predicted overall nivolumab average exposures across subjects with a wide range of body weight from 480 mg Q4W to be similar to that from 3 mg/kg Q2W. Although the flat dose is expected to lead to higher exposure in lighter patients relative to the exposure in heavier patients given the relationship between nivolumab PK and body weight, the predicted median and 95th percentile of exposures are maintained below those with 10 mg/kg every 2 weeks, which was established as a safe and well-tolerable dose across multiple tumor types. There was no clinical meaningful relationship between nivolumab exposure or body weight and frequency or severity of AEs. Therefore, a flat dose of 480 mg every 4 weeks is expected to be safe and tolerable in those patients. In terms of efficacy, 480 mg Q4W is expected to result in similar efficacy given the flat exposure-response relationship and same dose intensity. Overall, the benefit-risk profile of nivolumab 480 mg Q4W is expected to be similar to approved regimen 3 mg/kg Q2W and is therefore offered as an alternative dosing regimen.
1.4.4.4  **Rationale for Shorter Infusion Time for Nivolumab**

Long infusion times place a burden on subjects and treatment centers. Establishing that nivolumab can be safely administered using a shorter infusion time of 30 minutes duration will diminish this burden. Previous clinical studies of nivolumab monotherapy have used a 60 minute infusion duration for 1 to 3 mg/kg. However, nivolumab has been administered at up to 10 mg/kg with the same infusion duration.

Nivolumab has been administered safely over 60 minutes at doses ranging up to 10 mg/kg over long treatment durations. In study CA209-010 (a Phase 2, randomized, double blinded, dose ranging study of nivolumab in subjects with advanced/metastatic Renal Cell Carcinoma (RCC)) a dose association was observed for infusion site reactions and hypersensitivity reactions (1.7% at 0.3 mg/kg, 3.7% at 2 mg/kg and 18.5% at 10 mg/kg). All the events were Grade 1 to 2 and were manageable. An infusion duration of 30 minutes for 3 mg/kg nivolumab (30% of the dose provided at 10 mg/kg) is not expected to present any safety concerns compared to the prior experience at 10 mg/kg nivolumab dose infused over a 60-minute duration. 240 mg or 3 mg/kg infusion over 30 minutes results in a lower rate of infusion per mg than does 10 mg/kg infusion over 60 minutes, a dosing regimen that was found to be safe in a Phase 1 study across multiple tumor types (CA209003) and RCC study CA209010. Additionally, a dose of 480mg (~60% of a 10 mg/kg dose previously administered over 60 min) administered over 30 min is not anticipated to alter the safety profile. Nivolumab 480 mg over 30 min is being evaluated in this study as well as other clinical studies. As of Sep 2016, 4 patients in the nivolumab clinical development programs have received nivolumab 480 mg Q4W for at least 1 dose. BMS has a clinical safety program that monitors symptoms of potentially related to infusion-related reactions reported on the day of infusion and the following day. For the 4 patients treated with 480 mg 30-minute infusions there have been no reports of any symptoms that may potentially be linked to infusion reactions on the day of infusion or the following day.

Overall, infusion reactions including high-grade hypersensitivity reactions have been uncommon across nivolumab clinical studies, and no change in safety profile is anticipated with 30 minute infusion time.

1.4.4.5  **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 was a rare phenomenon observed in the Phase 1 study of BMS-936558 (nivolumab). 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.

1.4.4.6 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 using a prototype assay indicate PD-L1 expression in tumors may correlate with BMS-936558 (Nivolumab) clinical activity. Tumor biopsy specimens from a subset (N = 42) of subjects, including eighteen (18) melanoma subjects, in CA209003 were assessed for tumor PD-L1 expression measured by immunohistochemistry (IHC). In this limited data set, 100% of subjects whose tumors lacked PD-L1 expression (N = 18) did not have evidence of clinical benefit to BMS-936558 (Nivolumab), whereas subjects who had PD-L1 positive tumors were more likely to demonstrate clinical benefit. Amongst the melanoma subjects, the negative predictive value remained 100% (0/3) while the positive predictive value was 40% (6/15).41

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 this new diagnostic assay, the sponsor has assessed additional tumor biopsy specimens from CA209003 melanoma subjects for PD-L1 expression. Of this analysis of thirty-four (34) melanoma subjects, both biomarker and response evaluable, a signal consistent with that observed by Topalian et al was seen whereby a majority (7/10) of the objective responses were observed within the PD-L1 positive subset (68% of the evaluable population). Objective responses were noted 16% (3/18) PD-L1 negative or indeterminate populations. In this analysis, PD-L1 positivity was defined as a tumor specimen with ≥ 5% tumor cell membrane staining and using this cut-off. Forty-seven percent of melanoma subjects were defined as PD-L1 positive.

A prospective assessment of PD-L1 status within tumor biopsies will be conducted. There is evidence to suggest that PD-L1 expression may be both prognostic and predictive. One of the stratification factors will therefore be PD-L1 expression in order to attempt to decrease potential prognostic biases and also increase the ability to evaluate the predictive value of PD-L1 for response to BMS-936558 (Nivolumab).

1.5 Overall Risk/Benefit Assessment

There remains an unmet medical need for patients with previously untreated, unresectable or metastatic melanoma. This is illustrated by the fact that dacarbazine, the most commonly used approved standard of care agent for patients with previously untreated, BRAF wild-type
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melanoma in many parts of the world, including the EU, has not been shown to improve survival. BMS-936558 (Nivolumab) 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. BMS-936558 (Nivolumab) has also demonstrated a manageable safety profile. The most common AEs included fatigue, rash, pruritis, diarrhea, and nausea. The robust clinical activity demonstrated by BMS-936558 (Nivolumab) 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 BMS-936558 (Nivolumab) 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 BMS-936558 (Nivolumab) plus placebo vs dacarbazine plus placebo in adult (≥ 18 years) subjects with previously untreated, unresectable or metastatic melanoma. Subjects must be BRAF wild-type. Tumor tissue from an unresectable or metastatic site of disease must be analyzed and evaluable for PD-L1 status during the screening period in order to be randomized. Subjects must have unresectable Stage III or Stage IV melanoma as per the 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 if completed at least 6 weeks prior to randomization.

Subjects will be randomized 1:1 and stratified by PD-L1 status and 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)

- M stage (see Appendix 1)
  - M0/M1a/M1b vs
  - M1c

Subjects will be treated with BMS-936558 (Nivolumab) 3 mg/kg IV every 2 weeks plus placebo IV every 3 weeks or dacarbazine using the standard dose and schedule (1000 mg/m² IV every 3 weeks) plus placebo IV every 2 weeks. Subjects who receive BMS-936558 (Nivolumab) will receive a placebo that closely matches dacarbazine and is administered as per dacarbazine dosing guidelines, while subjects who receive dacarbazine will receive a placebo that closely matches BMS-936558 (Nivolumab) and is administered as per BMS-936558 (Nivolumab) dosing guidelines. Each cycle will be approximately 6 weeks in duration (3 doses of BMS-936558 (Nivolumab) or BMS-936558 (Nivolumab)-matched placebo and 2 doses of dacarbazine or dacarbazine-matched placebo per cycle). If a dose delay for more than 2 days is required, the
dose will be skipped and not replaced. In the event that a dose is skipped, treatment should resume with the next scheduled dose if the subject is eligible for further treatment at that time. Dose reductions will be allowed for dacarbazine or dacarbazine-matched placebo, but not for BMS-936558 (Nivolumab) or BMS-936558 (Nivolumab)-matched placebo. On-study tumor assessments will begin 9 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 an investigator-assessed clinical benefit and is tolerating study drug. The primary endpoint of this study is OS in all randomized subjects. Secondary endpoints include PFS in all randomized subjects, ORR in all randomized subjects, OS based on PD-L1 expression level, and mean changes from baseline in the EORTC QLQ-C30 global health status/QoL composite scale. Investigator assessments using RECIST 1.1 criteria will be utilized for PFS and response-based endpoints.

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

**Figure 3.1-1: Study Design Schematic**

Unresectable or metastatic melanoma:
- Previously untreated
- BRAF wild-type
- Tissue available for PD-L1 testing

Stratify by:
- PD-L1 status
- Positive vs. negative/indeterminate
- M stage
  - M0/M1a/M1b vs. M1c

BMS-936558
- 3 mg/kg IV every 2 weeks + Placebo IV every 3 weeks*

Dacarbazine
- 1000 mg/m² IV every 3 weeks + Placebo IV every 2 weeks*

Treat until progression** or unacceptable toxicity

1st Endpoint: OS

* Subjects who receive BMS-936558 will also receive a dacarbazine-matched placebo, while subjects who receive dacarbazine will also receive a BMS-936558-matched placebo.

** Treatment beyond initial investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

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). This study permits the re-enrollment of a subject that has discontinued the study as a pre-treatment failure (ie, subject has not been randomized / has not been treated). If re-enrolled, the subject must be re-consented
- Formalin-fixed and paraffin-embedded (FFPE) tumor tissue from an unresectable or metastatic site of disease must be available and sent to a central laboratory for biomarker
analyses. PD-L1 status must be determined prior to randomization and will be used as a stratification factor. PD-L1 status must be classified as positive, negative or indeterminate in order to be randomized. If an insufficient amount of recently acquired 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 fresh tumor tissue by study personnel for performance of biomarker analyses.

- A pregnancy test should be documented within 24 hours prior to the start of investigational product.
- Subject is assessed for complete study eligibility within the required timeframe found in Table 5.1.1-1.

Treatment Phase:

- Begins with the randomization call to the IVRS. The subject is randomly assigned to either the BMS-936558 (Nivolumab) + placebo arm (Arm A) or the dacarbazine + placebo arm (Arm B).

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 5.1.1-2.

- On-study laboratory assessments (Cycle 2 and beyond) should be drawn within 72 hours prior to dosing.
- Within 3 days from randomization the subject must receive the first dose of study medication (Day 1 of Cycle 1).
- Adverse event assessments should be documented at each clinic visit and WOCBP must have a pregnancy test during Week 1 and Week 4 of each cycle following Day 1 of treatment.

PK samples and immunogenicity samples will be collected according to the schedule in Table 5.5-1.

Subjects on the BMS-936558 (Nivolumab) + placebo arm (Arm A) are dosed with BMS-936558 (Nivolumab) every 2 weeks and placebo every 3 weeks (Table 5.1.1-2). Subjects on the dacarbazine + placebo arm (Arm B) are dosed with dacarbazine every 3 weeks and placebo every 2 weeks (Table 5.1.1-2).

- Treated subjects will be evaluated for response according to the RECIST 1.1 guidelines beginning 9 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.
Amendment 07 Update

As of 01-Jul-2014, all subjects were unblinded based on the recommendation of the Data Monitoring Committee (DMC). With this amendment, all subjects randomized to the dacarbazine arm who qualify for nivolumab therapy may enter the Nivolumab Open-Label Extension phase, as described below:

Nivolumab Open-Label Phase (schema for those previously randomized to dacarbazine):

- **Subjects previously randomized to Arm B (dacarbazine + placebo) of Study CA209066**
  - Must meet eligibility criteria for Nivolumab Extension Phase

  - **BMS-936558**
    - 3 mg/kg IV every 2 weeks
    - Treat until progression* or unacceptable toxicity

*Treatment beyond investigator-assessed RECIST 1.1-defined progression will be considered in subjects experiencing investigator-assessed clinical benefit and tolerating study therapy. Such subjects must discontinue therapy when further progression is documented.

1. Subjects treated with dacarbazine who have ended study treatment will be able to receive treatment with nivolumab via the Open-Label phase of the study, assuming basic inclusion/exclusion criteria are met (including a 3-week washout period for subsequent ipilimumab or a 2-week washout period for other subsequent therapy). Details provided in Sections 3.3.1 and 3.3.2.

2. Subjects still being treated with dacarbazine will continue to be treated and monitored as specified in the protocol as long as they are continuing to derive benefit from dacarbazine in the judgment of the investigator. These subjects may receive nivolumab once they are discontinued from dacarbazine therapy, assuming basic inclusion/exclusion criteria are met (including a 2-week washout period from last dose of dacarbazine).

3. Subjects currently treated with nivolumab will continue to be treated and monitored as specified in the protocol. Details provided Sections 3.3.1 and 3.3.2.

Table 5.1.2-1, Table 5.1.2-2, and Table 5.1.2-4 describe screening and on-study assessments for the open-label phase.
All subjects currently receiving nivolumab or eligible to receive nivolumab 3 mg/kg dosing will have the option to switch to 480 mg flat dose every 4 weeks. Switch to flat does is optional. Subjects agreeing to switch to 480 mg flat dose every 4 weeks will have to be re-consented prior to initiation of flat dosing. Once re-consented, the subject will receive a flat dose of 480 mg nivolumab IV every 4 weeks, beginning two weeks after the last dose of weight-based nivolumab. The flat dose option of nivolumab is also valid for subjects who discontinued from the dacarbazine open label treatment and meet eligibility criteria (including a 3-week washout period for subsequent ipilimumab or a 2-week washout period for other subsequent therapy) for nivolumab extension phase described in section 3.3.2. Once re-consented, the subject will receive a flat dose of 480 mg nivolumab IV every 4 weeks.

- PK samples and immunogenicity samples will not be collected for patients on the weight based dose of Nivolumab. PK samples and immunogenicity samples will be collected in patients on the flat dose of nivolumab according to the schedule in Table 5.5-2.

- 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 disease progression is documented.

Follow-Up Phase

- Begins when the decision to discontinue a subject from study therapy is made (no further treatment with study therapy).

Table 5.1.2-5 and Table 5.1.2-6 describe follow-up assessments for the open-label phase.
Two follow-up visits (referred to as X visits in Table 5.1.1-3) include collection of PK/immunogenicity samples.

- Subjects who discontinue treatment for reasons other than tumor progression will continue to have tumor assessments beginning 9 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.

- Subjects will be followed for drug-related toxicities until these toxicities resolve, return to baseline or are deemed irreversible. All toxicities will be documented for a minimum of 100 days after last dose.

- After completion of the two X 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 treated/randomized subjects outside of the protocol defined window as detailed in the Time and Events Table 5.1.2-5 Follow-up Assessments (CA209066) and Table 5.1.2-6. 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 5.1.1-3.

The total duration of the study from start of randomization to final analysis of OS was expected to be 30 months (9.5 months of accrual + 20.5 months of follow-up), assuming a constant accrual of 43 subjects per month. 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.

**Amendment 09 Update**

- PK samples and immunogenicity samples will not be collected during the follow-up phase for patients on the weight based and flat dosing of nivolumab

- 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 disease progression is documented.

- PRO (Patient Reported Outcome) instruments will now be completed every 6 months rather than every 3 months during the follow-up phase.
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-Blinded Study Phase

1. Signed Written Informed Consent
   a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
   b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study.

2. Target Population
   a) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (Appendix 2).
   b) Untreated, histologically confirmed unresectable Stage III or Stage IV melanoma, as per AJCC staging system. 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.
   c) Measurable disease by CT or MRI per RECIST 1.1 criteria.
   d) 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 recently acquired 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 fresh tumor tissue by study personnel for performance of biomarker analyses.
   e) Known BRAF wild-type as per regionally acceptable V600 mutational status testing. BRAF mutant subjects and those with indeterminate or unknown BRAF status are not permitted to randomize.
   f) Prior palliative radiotherapy must have been completed at least 2 weeks prior to study drug administration.
g) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:

i) WBC \( \geq 2000/\mu L \)

ii) Neutrophils \( \geq 1500/\mu L \)

iii) Platelets \( \geq 100 \times 10^3/\mu L \)

iv) Hemoglobin \( > 9.0 \text{ g/dL} \)

v) Creatinine Serum creatinine \( \leq 1.5 \times \text{ULN} \) or creatinine clearance (CrCl) \( \geq 40 \text{ mL/min} \) (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 \( \leq 3 \times \text{ULN} \) (\( \leq 5 \times \text{ULN} \) for subjects with liver metastases)

vii) Bilirubin \( \leq 1.5 \times \text{ULN} \) (except subjects with Gilbert Syndrome, who can have total bilirubin \( < 3.0 \text{ mg/dL} \)).

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

3. Age and Reproductive Status

a) Men and women, age \( \geq 18 \) years

b) Women of childbearing potential (WOCBP) must use method(s) of contraception based on the tables in Appendix 3. Dacarbazine is teratogenic. There is an insufficient amount of information to assess teratogenicity for BMS-936558 (Nivolumab). 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. Given the blinded nature of this study, WOCBP should therefore use an adequate method to avoid pregnancy for 5 months (30 days plus the time required for BMS-936558 (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 (see Appendix 3). 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. Given the blinded nature of the study, men who are sexually active with WOCBP must continue contraception for 7 months (90 days plus the time required for BMS-936558 (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 3.3.5 for the definition of WOCBP) and azoospermic men do not require contraception.

### 3.3.2 Inclusion Criteria for Entering the Nivolumab Open-Label Extension Phase Subjects Previously Randomized to Dacarbazine

1. **Signed Written Informed Consent**
   a) Subjects must have signed and dated an IRB/IEC approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol-related procedures that are not part of normal subject care.
   b) Subjects must be willing and able to comply with scheduled visits, treatment schedule, laboratory tests, and other requirements of the study

2. **Target population**
   a) Prior anti-cancer therapy, including dacarbazine and palliative radiotherapy, must have been completed at least 2 weeks prior to study drug administration. Prior ipilimumab must have been completed at least 3 weeks prior to study drug administration.
   b) Adverse events related to any prior anti-cancer therapy must have resolved to Grade 1 or baseline.
   c) Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:
      i) WBC $\geq 2000/\mu L$
      ii) Neutrophils $\geq 1500/\mu L$
      iii) Platelets $\geq 100\times 10^3/\mu L$
      iv) Hemoglobin $> 9.0$ g/dL
v) Creatinine Serum creatinine $\leq 1.5 \times \text{ULN}$ or creatinine clearance (CrCl) $\geq 40 \text{mL/min}$ (using the Cockcroft-Gault formula):

Female CrCl = \( (140 - \text{age in years}) \times \text{weight in kg} \times 0.85 \)
\[
72 \times \text{serum creatinine in mg/dL}
\]
Male CrCl = \( (140 - \text{age in years}) \times \text{weight in kg} \times 1.00 \)
\[
72 \times \text{serum creatinine in mg/dL}
\]

vi) AST/ALT $\leq 3 \times \text{ULN}$ ($\leq 5 \times \text{ULN}$ for subjects with liver metastases)

vii) Bilirubin $\leq 1.5 \times \text{ULN}$ (except subjects with Gilbert Syndrome, who can have total bilirubin $< 3.0 \text{mg/dL}$).

3.3.3 Exclusion Criteria-Blinded Study Phase

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. 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 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.

b) 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.

c) 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.

d) 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.

e) Any major surgery (eg, hip or spine surgery) less than 28 days prior to the first dose of study drug.
f) Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways.

g) Uncontrolled adrenal insufficiency.

3. Physical and Laboratory Test Findings

a) Positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test 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.

3.3.4 Exclusion Criteria for Entering the Nivolumab Open-Label Extension Phase-Subjects Previously Randomized to Dacarbazine

1. Medical History and Concurrent Diseases

a) Known positive test for hepatitis B virus (HBV) using HBV surface antigen (HBV sAg) test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection.

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) 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.
d) 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.

e) Any major surgery (eg, hip or spine surgery) less than 28 days prior to the first dose of study drug.

f) Prior treatment with an anti-PD-1 or anti-PD-L1 therapy.

g) Uncontrolled adrenal insufficiency.

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.

3.3.5 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 > 40 mIU/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 3.4.2 or to treat a drug-related adverse event).
- Any concurrent antineoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, extensive radiation therapy, or standard or investigational agents for treatment of cancer).

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

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

1) The lesion being considered for palliative therapy is not a target lesion.
2) 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).
3) The case is discussed with the BMS medical monitor.
Palliative therapy must be clearly documented as such in the study record.

Surgical resection of lesions is otherwise not permitted.

Subjects may continue to receive hormone replacement therapy if initiated prior to randomization. Bisphosphonates and RANK-L inhibitors are allowed for bone metastases if initiated prior to randomization.

Dacarbazine is metabolized by cytochrome P450 (CYP1A1, CYP1A2 and CYP2E1). This has to be taken into account if other drugs are co-administered which are metabolized by the same hepatic enzymes.

Hepatotoxic drugs and alcohol should be avoided.

### 3.4.2 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 specific 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 Assessments and Procedures. The only exception to this requirement is when a subject withdraws consent for all study procedures.
including post-treatment study follow-up or loses the ability to consent freely (i.e., 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 Procedures and Assessments, 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 (e.g., 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**

<table>
<thead>
<tr>
<th>Product Description and Dosage Form</th>
<th>Potency</th>
<th>Primary Packaging (Volume)/Label Type</th>
<th>Secondary Packaging (Qty)/Label Type</th>
<th>Appearance</th>
<th>Storage Conditions (per label)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS-936558 (Nivolumab) Solution for Injection</td>
<td>100 mg (10 mg/mL)</td>
<td>10 mL per vial/Open-Label</td>
<td>10 vials per carton/Open-label</td>
<td>Clear to opalescent colorless to pale yellow liquid. May contain particles</td>
<td>2 to 8°C. Protect from light and freezing.</td>
</tr>
<tr>
<td>Dacarbazine Powder for IV solution</td>
<td>200 mg/vial&lt;sup&gt;a&lt;/sup&gt;</td>
<td>200 mg per vial/Open-label</td>
<td>10 vials per carton/Open-label</td>
<td>White to pale yellow powder</td>
<td>Do not store above 25°C. Protect from light.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dacarbazine may be obtained by the investigational sites in certain countries as local commercial product (which may be available as a different potency/package size than listed above) if local regulations allow this. Locally sourced marketed product utilized for this study should be stored in accordance with the package insert, summary of product characteristics (SmPC), or equivalent document.

Premedications or medications used to treat infusion-related reactions will be sourced by the investigative sites.
4.1.1  **Investigational Product**

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

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

In this protocol, investigational product(s) is/are: BMS-936558 (Nivolumab), dacarbazine

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: Matching placebo IV solution (0.9% sodium chloride or 5% glucose), premedications/medications referred to in Sections 4.3.1 and 4.3.6.

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).

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.

Locally sourced market product dacarbazine should be stored and prepared/administered in accordance with the package insert, summary of product characteristics (SmPC) or equivalent document.

BMS-936558 (Nivolumab) 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 BMS-936558 (Nivolumab) include laboratory coats and gloves.
The investigational sites are responsible for providing IV bags, diluents (0.9% sodium chloride or 5% glucose), filters, etc.

For details on prepared drug storage and use time of BMS-936558 (Nivolumab) under room temperature/light and refrigeration, please refer to the Investigator Brochure section for “Recommended Storage and Use Conditions”.

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 BMS-936558 (Nivolumab) and polyolefin bags have been observed.

BMS-936558 (Nivolumab) is to be administered as a 30-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.

A separate instruction sheet will be provided with preparation/handling instructions for dacarbazine IV solution.

Amendment 09 Update

Starting 2 weeks after the last dose of weight-based nivolumab, subjects who consent to switch to the flat dose nivolumab will be administered 480 mg nivolumab IV every 4 weeks (Q4W) over 30 minutes until unacceptable toxicity or disease progression.

In addition, regardless of the type of nivolumab dosing schedule (Weight based or flat dose), the duration of nivolumab infusion will be 30 minutes. Patients on the weight base infusion who were previously receiving the infusion over 60 minutes, will now be converted to a 30 minutes infusion.

4.2 Method of Assigning Subject Identification

The subject number will be assigned through an interactive voice response system (IVRS) once the subject has signed the informed consent form and is registered. Every subject that signs the informed consent form must be assigned a subject number in IVRS. Specific instructions for using IVRS will be provided to the investigational site in a separate document.

The investigator or designee will register the subject for enrollment by following the enrollment procedures established by BMS. The following information is required for enrollment:

- Date that informed consent was obtained
- Date of birth.

Once enrolled in IVRS, enrolled subjects that have signed the informed consent form and met all eligibility criteria will be ready to be randomized through the IVRS by the unblinded pharmacist/drug preparer. The following information is required for subject randomization:

- Subject number
• Date of birth
• 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)
  – PD-L1 indeterminate (tumor cell membrane scoring hampered by high cytoplasmic staining or melanin content)
• M Stage (see Appendix 1)

*To be entered by central lab rather than investigator

Subjects meeting all eligibility criteria will be randomized in a 1:1 ratio to Arm A (BMS-936558 (Nivolumab)) or Arm B (Dacarbazine), 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 1)
  – M0/M1a/M1b vs
  – M1c.

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

**Amendment 07 Update**

IVRS will be amended to allow subjects that were previously randomized to Arm B (dacarbazine), to be allowed to receive treatment with Nivolumab. This option is also valid for subjects that discontinued from the trial. The IVRS will assign the Nivolumab treatment for all subjects as originally designed in the system; however the placebo visit call is no longer necessary and can be skipped.

Subjects currently randomized to Arm B (dacarbazine) may also continue obtaining that treatment as previously through the IVRS as long as they are continuing to derive benefit from dacarbazine in the judgment of the investigator.

**Amendment 09 Update**

IVRS will be amended to allow subjects to receive nivolumab open treatment with 480mg every 4 weeks. This option is for subjects currently receiving nivolumab weight-based treatment and
also subjects discontinued from the dacarbazine open label treatment and meet eligibility criteria for nivolumab extension phase described in section 3.3.2.

4.3 Selection and Timing of Dose for Each Subject

<table>
<thead>
<tr>
<th>Table 4.3-1:</th>
<th>Blinded Study Dosing Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day1 Week 1</td>
<td>Day 1 Week 2</td>
</tr>
<tr>
<td>BMS-936558 (Nivolumab)(^a)</td>
<td>X</td>
</tr>
<tr>
<td>Dacarbazine (^a,b)</td>
<td>X</td>
</tr>
</tbody>
</table>

\(^a\) Or placebo version of respective drug  
\(^b\) Administer antiemetic premedication as per Section 4.3.1.

On Day 1 Week 1 of each cycle, BMS-936558 (Nivolumab) should always be administered before dacarbazine and doses should be separated by at least 1 hour.

For subjects on both arms, all doses should be rounded to the nearest milligram. The screening body weight may be used for dosing of cycle 1. Weight measured at Day 1 at every other cycle will be used for subsequent dosing. If the subject’s weight on the day of the dosing differs by > 10% from the weight used to calculate the dose, the dose should be recalculated. There will be no BMS-936558 (Nivolumab) or BMS-936558 (Nivolumab)-matched placebo dose modifications allowed. Dose modifications for dacarbazine or dacarbazine-matched placebo are allowed as described in Section 4.3.3. Subjects may be dosed no less than 12 days from the previous dose of BMS-936558 (Nivolumab) or 19 days from the previous dose of dacarbazine. If a subject cannot receive a dose within 2 days of its scheduled administration date, the dose should be completely skipped. When the subject is able to be re-treated, dosing should resume at the time of the next scheduled dose. Missed doses will not be replaced.

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

Subjects will be monitored continuously for AEs while on study. Treatment modifications (eg, the skipping of a dose) will be based on specific laboratory and adverse event criteria.
Amendment 09 Update

Table 4.3-2: Unblinded Study Dosing Schedule

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 1</td>
<td>Week 2</td>
<td>Week 3</td>
<td>Week 4</td>
<td>Week 5</td>
</tr>
<tr>
<td>BMS-936558 arm</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>(Nivolumab) 3mg/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>every 2 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMS-936558 arm (Nivolumab) 480mg flat dose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>every 4 weeks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dacarbazine arm</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>a,b</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Active drug
b Administer antiemetic premedication as per Section 4.3.1.

The subjects in the nivolumab arm will be dosed every two weeks if on the weight-based dosing, and every 4 weeks if on the flat dosing. The subjects on dacarbazine will be dosed every three weeks. The first flat dose 480 mg nivolumab will be administered 2 weeks after the last dose of nivolumab weight-based. A cycle will be 4 weeks under the flat dosing nivolumab, while it will remain 6 weeks long for patients staying on the weight-based nivolumab.

There will be no nivolumab dose modification allowed. Dose modifications for open-label dacarbazine are allowed as described in Section 4.3.3.

Subjects on the weight-based nivolumab may be dosed no less than 12 days from the previous dose of nivolumab or 19 days from the previous dose of dacarbazine. If a subject cannot receive a dose within 2 days of its scheduled administration date, the dose should be completely skipped. When the subject is able to be re-treated, dosing should resume at the time of the next scheduled dose. Missed doses will not be replaced.

Subjects on the flat dose of nivolumab may be dosed up to 3 working days after the scheduled date if necessary, but no less than 26 days from the previous dose. Subsequent dosing should be based on the actual date of administration of the previous dose of drug. Every effort should be made to adhere to protocol treatment schedule of administration of nivolumab every 4 weeks. In extenuating circumstances in which the patient cannot make the dosing schedule within the 3 working days window, BMS Study Director or Medical Monitor should be contacted.

4.3.1 Antiemetic Premedications

Antiemetic premedications should be administered prior to dosing of dacarbazine or dacarbazine-matched placebo. The following antiemetic premedications are acceptable and should be administered as per local standards: H2 receptor blockers (eg, ranitidine), 5-HT3

Revised Protocol No.: 05
Date: 23-Sep-2016

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antagonists (eg, palonosetron, ondansetron), metoclopramide, and substance P antagonists
(eg, aprepitant). Steroids should not be administered unless a subject continues to have
symptoms despite the use of the acceptable antiemetics mentioned above.

Antiemetic premedications should not be routinely administered prior to dosing of BMS-936558
(Nivolumab) and BMS-936558 (Nivolumab)-matched placebo.

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 BMS-936558 (Nivolumab), dacarbazine, or both). All study drugs must be
delayed until treatment can resume (see Section 4.3.4). If administration of a study drug is
delayed more than 2 days for subjects on dacarbazine or weight-based nivolumab, the dose
should be completely skipped and the subject should continue to follow the standard dosing
schedule (Table 4.3-1).

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

BMS-936558 (Nivolumab) and dacarbazine 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.

If dosing is delayed past the start date of the next cycle, Day 1 Week 1 of the subsequent cycle
will be delayed until dosing resumes.

Amendment 09 update

If administration of study drug is delayed more than 3 business days for subjects on nivolumab
flat dose, the dose should be completely skipped and the subject should continue to follow the
standard dosing schedule (Table 4.3-1).

4.3.3 Dose Modifications

Dose reductions or dose escalations are not permitted for BMS-936558 (Nivolumab).
Dose escalations are not permitted for dacarbazine.

Dacarbazine should be dose-reduced at the time of the next scheduled dose as per Table 4.3.3-1 if:

- The prior dose was skipped due to a Grade 3 drug-related hematologic adverse event or a recurrent Grade 2 drug-related hematologic adverse event.
- The prior dose was skipped due to a drug-related 2-grade shift in AST, ALT, or total bilirubin.

### Table 4.3.3-1: Dose Reductions for Dacarbazine

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Dose Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting Dose</td>
<td>1000 mg/m²</td>
</tr>
<tr>
<td>1st Dose Reduction</td>
<td>750 mg/m²</td>
</tr>
<tr>
<td>2nd Dose Reduction</td>
<td>500 mg/m²</td>
</tr>
<tr>
<td>3rd Dose Reduction</td>
<td>Stop Drug</td>
</tr>
</tbody>
</table>

Dacarbazine may be dose-reduced for other reasons if discussed with and agreed to by the BMS Medical Monitor.

All dose modification rules also apply for the placebo version of each agent, given the blinded nature of this study. Not applicable once study treatment has been unblinded.

### 4.3.4 Criteria to Resume Treatment

All criteria to resume treatment for BMS-936558 (Nivolumab) and dacarbazine also apply for the placebo version of each agent, given the blinded nature of this study. Not applicable once study treatment has been unblinded.

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 AST/ALT or total bilirubin in the Grade 1 toxicity range 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 treatment is delayed > 6 weeks from the scheduled dosing of nivolumab weight-based or dacarbazine treatment, the subject must be permanently discontinued from study therapy, except as specified in Section 4.3.5.

Treatment should only be resumed at the time of the next scheduled dose. Skipped doses are not to be replaced.

As stated in Section 4.3.5, subjects who require dacarbazine or dacarbazine-matched placebo dose reduction below 500 mg/m² must be permanently discontinued, even if they otherwise meet criteria to resume treatment.

**Amendment 09 update**

Subjects receiving nivolumab flat dosing who meet criteria for discontinuation may resume weight based dosing at 3mg/kg every 2 weeks when the drug related AE(s) resolve(s) to Grade ≤ 1 or baseline, after discussion and approval by the BMS Medical Monitor/designee.

If treatment is delayed > 10 weeks from the scheduled dosing of nivolumab flat dose treatment, 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 BMS-936558 (Nivolumab) and dacarbazine 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, hypersensitivity reactions, and infusion reactions:
  - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, 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 > 5-10x ULN for > 2 weeks
- AST or ALT > 10x ULN
- Total bilirubin > 5x ULN
- Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
- 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 for subjects receiving nivolumab weight-based dosing or dacarbazine 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 toxicity requiring dacarbazine or dacarbazine-matched placebo dose reduction below 500 mg/m²

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 study drug dosing.

Amendment 09 update

Any dosing interruption lasting > 10 weeks for subjects receiving nivolumab flat dosing 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 > 10 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
- Dosing interruptions > 10 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 > 10 weeks, the BMS medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted.
4.3.6 **Treatment of BMS-936558 (Nivolumab) Related Infusion Reactions**

Since BMS-936558 (Nivolumab) 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.

Given the blinded nature of this study, all of the treatment recommendations provided below are relevant for BMS-936558 (Nivolumab), as well as BMS-936558 (Nivolumab) matched placebo.

**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 BMS-936558 (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 BMS-936558 (Nivolumab) 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 BMS-936558 (Nivolumab) 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 BMS-936558 (Nivolumab) 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 [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilatory support indicated).

Immediately discontinue infusion of BMS-936558 (Nivolumab). 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. BMS-936558 (Nivolumab) 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 (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

### 4.3.7 Treatment Beyond Progression

As described in Section 1.4.4.5, accumulating evidence indicates a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of PD.\(^{42}\)

Subjects will be permitted to continue study treatment beyond initial RECIST 1.1 defined PD as long as they meet the following criteria:

- Investigator-assessed clinical benefit
- 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

The Sponsor, subjects, investigator and site staff will be blinded to the study drug administered (BMS-936558 (Nivolumab) or Dacarbazine). 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.

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. The subject’s safety takes priority over any other considerations in determining if a treatment assignment should be unblinded.

Before breaking the blind of an individual subject's treatment, the investigator should determine that the unblinded information is necessary, 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 be discussed with the Medical Monitor, but the investigator always has ultimate authority for the decision to unblind.

For this study, the method of unblinding for emergency purposes is through the IVRS. For information on how to unblind for emergency, please consult the IVRS manual.

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

Any request to unblind a subject for non-emergency purposes 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.

**Amendment 07 Update**

The section above pertained to the blinded phase of the study only.
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 (e.g., 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, i.e., 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

5.1.1 Blinded Treatment Phase

Table 5.1.1-1: Screening Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening Visit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eligibility Assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td>All inclusion/exclusion criteria should be assessed at screening and confirmed prior to randomization</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tumor Tissue Samples</td>
<td>X</td>
<td>Tumor tissue from an unresectable or metastatic site must be available and are to be sent to a central laboratory for biomarker analyses. PD-L1 status will be assessed prior to randomization and will serve as one of the stratification factors (PD-L1 positive vs PD-L1 negative/indeterminate).</td>
</tr>
<tr>
<td>BRAF Status</td>
<td>X</td>
<td>If not available prior to enrollment</td>
</tr>
<tr>
<td>Safety Assessments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>Including height, weight, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion. To be performed within 3 days prior to randomization.</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assessment of Signs and Symptoms</td>
<td>X</td>
<td>Within 14 days prior to randomization</td>
</tr>
<tr>
<td>Baseline Adverse Events Assessment</td>
<td>X</td>
<td>Within 14 days prior to randomization</td>
</tr>
<tr>
<td>Concomitant Medication Collection</td>
<td>X</td>
<td>Within 14 days prior to randomization</td>
</tr>
</tbody>
</table>
Table 5.1.1-1:  Screening Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening Visit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td>On site/local CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, endocrine panel (TSH, Free T4, Free T3), Hep B/C (HBV sA and HCV RNA or HCV antibody test), within 14 days prior to randomization.</td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td>Within 24 hours prior to first dose.</td>
</tr>
<tr>
<td>Efficacy Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening/baseline Tumor Assessment</td>
<td>X</td>
<td>Chest, Abdomen, Pelvis and Brain within 28 days prior to first dose. Head MRI is required in subjects with known history of brain metastases; subjects without known history of brain metastases may have head CT or MRI.</td>
</tr>
</tbody>
</table>
### Table 5.1.1-2: On-Study Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>9 Weeks from Randomization and then Every 6 Weeks (± 1 Week)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 22</td>
</tr>
<tr>
<td>Eligibility Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Safety Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of Concomitant Medications</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Refer to Table 5.5-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Samples</td>
<td>Refer to Table 5.5-1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LFTs, Creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
# Table 5.1.1-2: On-Study Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>9 Weeks from Randomization and then Every 6 Weeks (± 1 Week)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 22</td>
</tr>
<tr>
<td><strong>Efficacy Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Exploratory Testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum (for soluble factors)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood RNA</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood Mononuclear Cells</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Whole blood</td>
<td>Any time after randomization</td>
<td></td>
<td>EDTA Tubes for DNA</td>
</tr>
<tr>
<td><strong>Outcomes Research Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tumor assessments should first be performed at 9 weeks (± 1 wk) following randomization then every 6 weeks (± 1 wk) thereafter for the first 12 months and then every 12 weeks (± 1 wk) until disease progression or treatment discontinuation. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline.
### Table 5.1.1-2: On-Study Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>9 Weeks from Randomization and then Every 6 Weeks (± 1 Week) (Refer to Notes)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 22</td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical Drug Supplies</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomize</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Administer Study Drug</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
### Table 5.1.1-3: Follow-Up Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X, Follow-Up&lt;sup&gt;a&lt;/sup&gt; Visits 1 and 2</th>
<th>Y, Survival Follow-Up&lt;sup&gt;b&lt;/sup&gt; Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td><strong>To assess for potential late emergent study drug related issues</strong></td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td>X</td>
<td>X</td>
<td><strong>For study drug related adverse events only</strong></td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td></td>
<td><strong>On site/local CBC w/differential, LFTs, BUN or serum urea level, creatinine, and TSH for X01, repeat at X02 if study drug related toxicity persists.</strong></td>
</tr>
<tr>
<td>Review of Concomitant Medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunogenicity Blood Sample</td>
<td>X</td>
<td></td>
<td><strong>Refer to Table 5.5-1</strong></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td></td>
<td><strong>On site/local Serum or Urine</strong></td>
</tr>
<tr>
<td><strong>Pharmacokinetic (PK) Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PK Samples</td>
<td>X</td>
<td></td>
<td><strong>Refer to Table 5.5-1</strong></td>
</tr>
<tr>
<td><strong>Outcomes Research Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td></td>
<td><strong>Follow up visits 1 and 2 only</strong></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>X</td>
<td><strong>Follow up visits 1 and 2, and survival visits every 3 months for the next 12 months, then every 6 months thereafter (may be accomplished by visit or phone contact, for Y visits only).</strong></td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td></td>
<td><strong>Follow up visits 1 and 2 only</strong></td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td></td>
<td><strong>Follow up visits 1 and 2 only</strong></td>
</tr>
<tr>
<td><strong>Survival Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Status</td>
<td>X</td>
<td>X</td>
<td><strong>Every 3 months, may be accomplished by visit (or phone contact for Y visits), to include subsequent anti-cancer therapy</strong></td>
</tr>
</tbody>
</table>
## Table 5.1.1-3: Follow-Up Assessments (CA209066)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X, Follow-Up&lt;sup&gt;a&lt;/sup&gt; Visits 1 and 2</th>
<th>Y, Survival Follow-Up&lt;sup&gt;b&lt;/sup&gt; Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy Assessments</strong></td>
<td></td>
<td></td>
<td>Only for subjects without progression on study therapy. Tumor assessments should first be performed at 9 weeks (± 1 wk) following randomization then every 6 weeks (± 1 wk) thereafter for the first 12 months, and then every 12 weeks (± 1 wk) until disease progression is documented. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline.</td>
</tr>
<tr>
<td>Tumor Assessments</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> X visits occur as follows - X1 = 30 days from last dose ± 7 days, X2 = 70-84 days from X1. X1 may occur later if treatment has been delayed before discontinuation.

<sup>b</sup> Y, Survival visits continue every 3 months after X visits
## 5.1.2 Open - Label Treatment Phase

### Table 5.1.2-1: Screening Assessments (CA209066) for Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase (Nivolumab Open-Label Extension Phase)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening Visit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eligibility Assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>X</td>
<td>Inclusion/exclusion criteria should be assessed at screening and confirmed prior to starting open-label study treatment. This is only applicable to subjects randomized to dacarbazine now entering the nivolumab Open-Label Extension Phase</td>
</tr>
<tr>
<td>Medical History</td>
<td>X</td>
<td>Report conditions not related to melanoma if not reported at screening in blinded study phase</td>
</tr>
<tr>
<td>Tumor Tissue Samples</td>
<td>X</td>
<td>If medically safe and/or feasible, tumor tissue should be collected after dacarbazine treatment: sample may be a recent biopsy or an archival sample that is formalin-fixed and paraffin-embedded</td>
</tr>
<tr>
<td><strong>Safety Assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Examination</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>Including height, weight, BP, HR, temperature and oxygen saturation by pulse oximetry at rest and after exertion. To be performed within 3 days prior to starting the nivolumab Open-Label Phase</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Assessment of Signs and Symptoms</td>
<td>X</td>
<td>Within 14 days prior to starting nivolumab Open-Label Extension Phase. Report conditions related to the melanoma or its prior treatment</td>
</tr>
<tr>
<td>Concomitant Medication Collection</td>
<td>X</td>
<td>Within 14 days prior to starting nivolumab Open-Label Extension Phase</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td>On site/local CBC w/differential, Chemistry panel including: LDH, AST, ALT, ALP, T.Bili, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, Glucose, endocrine panel (TSH, Free T4, Free T3), within 14 days prior to starting nivolumab Open-Label Extension Phase</td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td>Within 24 hours prior to first dose.</td>
</tr>
</tbody>
</table>
## Table 5.1.2-1: Screening Assessments (CA209066) for Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase (Nivolumab Open-Label Extension Phase)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Screening Visit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening/baseline Tumor Assessment</td>
<td>X</td>
<td>Chest, Abdomen, Pelvis and Brain within 28 days prior to first dose. Head MRI is required in subjects with known history of brain metastases; subjects without known history of brain metastases may have head CT or MRI.</td>
</tr>
</tbody>
</table>
Table 5.1.2-2: Open-label Procedural Outline (CA209066) Nivolumab 3 mg/kg every 2 weeks Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>Every 6 Weeks (± 1 Week) (Refer to Notes)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 29</td>
</tr>
<tr>
<td>Safety Assessments</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of Concomitant Medications</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Efficacy Assessments</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Revised Protocol No.: 05  Date: 23-Sep-2016

Approved v6.0  930063436 8.0
### Table 5.1.2-2: Open-label Procedural Outline (CA209066) Nivolumab 3 mg/kg every 2 weeks Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>Every 6 Weeks (± 1 Week) (Refer to Notes)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 Day 15 Day 29</td>
<td>continue to be scanned until disease progression is documented.</td>
<td></td>
</tr>
<tr>
<td><strong>Exploratory Testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum (for soluble factors)</td>
<td>X X</td>
<td>Cycle 1 only <em>(for dacarbazine treated subjects that enter the nivolumab the Open-Label Extension Phase)</em> To be collected prior to dosing</td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood RNA</td>
<td>X X</td>
<td>Cycle 1 only <em>(for dacarbazine-treated subjects that enter the nivolumab the Open-Label Extension Phase)</em> To be collected prior to dosing</td>
<td></td>
</tr>
<tr>
<td>Peripheral Blood Mononuclear Cells</td>
<td>X X</td>
<td>Cycle 1 only <em>(for dacarbazine-treated subjects that enter the nivolumab the Open-Label Extension Phase)</em> To be collected prior to dosing</td>
<td></td>
</tr>
<tr>
<td><strong>Outcomes Research Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td>To be completed prior to dosing. *Not applicable to subjects previously randomized to dacarbazine*</td>
<td></td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>To be completed prior to dosing. *Not applicable to subjects previously randomized to dacarbazine*</td>
<td></td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td>To be completed prior to dosing. *Not applicable to subjects previously randomized to dacarbazine*</td>
<td></td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td>To be completed prior to dosing</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.1.2-2: Open-label Procedural Outline (CA209066) Nivolumab 3 mg/kg every 2 weeks Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>Every 6 Weeks (± 1 Week) (Refer to Notes)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 15</td>
<td>Day 29</td>
</tr>
<tr>
<td>Clinical Drug Supplies</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Administer Study Drug</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
**Table 5.1.2-3: Open-label Procedural Outline (CA209066) Nivolumab 480 mg every 4 weeks Arm**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q4 Weeks)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety Assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td>Physical examinations are to be performed as clinically indicated.</td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>Including BP, HR, weight (Weight at Day 1 of each subsequent cycle only), temperature and oxygen saturation by pulse oximetry at rest and after exertion prior to dosing.</td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Review of Concomitant Medications</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Events Assessment</strong></td>
<td>Continuous</td>
<td>throughout the study</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td>Within 72 hours prior to dosing. On site/local CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, TSH (with reflexive free T4/free T3).</td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td>On site/local Serum or Urine : every 4 weeks +/- 1 week</td>
</tr>
<tr>
<td><strong>Efficacy Assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Assessments</td>
<td>Refer to notes</td>
<td>For patients who start flat dose without having been on nivolumab therapy before, tumor assessments will be done every 6 weeks (± 1 wk) for the first 12 months, then every 12 weeks until disease progression (after beginning nivolumab therapy) and nivolumab discontinuation. For patients who are switched from nivolumab weight based to flat dose, and who have been on nivolumab for ≤ 12months, tumor assessments will be done every 6 weeks (± 1 wk). After a total duration of nivolumab &gt; 12months, tumor assessment will be done every 12 weeks until disease progression (after beginning nivolumab therapy) and nivolumab discontinuation. 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 disease progression is documented. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline.</td>
</tr>
</tbody>
</table>
Table 5.1.2-3: Open-label Procedural Outline (CA209066) Nivolumab 480 mg every 4 weeks Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q4 Weeks)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetic (PK) Assessment</td>
<td></td>
<td><strong>PK Samples/immunogenicity</strong> X Refer to Table 5.5-2.</td>
</tr>
<tr>
<td>Exploratory Testing</td>
<td></td>
<td><strong>Cycle 1 only (for dacarbazine treated subjects that enter the Nivolumab the Open-Label Extension Phase)</strong> To be collected prior to dosing</td>
</tr>
<tr>
<td>Serum (for soluble factors)</td>
<td>X</td>
<td><strong>Cycle 1 only (for dacarbazine-treated subjects that enter the Nivolumab the Open-Label Extension Phase)</strong> To be collected prior to dosing</td>
</tr>
<tr>
<td>Peripheral Blood RNA</td>
<td>X</td>
<td>To be collected prior to dosing</td>
</tr>
<tr>
<td>Peripheral Blood Mononuclear Cells</td>
<td>X</td>
<td><strong>Cycle 1 only (for dacarbazine-treated subjects that enter the Nivolumab the Open-Label Extension Phase)</strong> To be collected prior to dosing</td>
</tr>
<tr>
<td>Outcomes Research Assessments</td>
<td></td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td>To be completed prior to dosing</td>
</tr>
</tbody>
</table>

Not applicable to subjects previously randomized to Dacarbazine.
Table 5.1.2-3: Open-label Procedural Outline (CA209066) Nivolumab 480 mg every 4 weeks Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q4 Weeks)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Drug Supplies</td>
<td></td>
<td><strong>First dose to be administered within 3 days of change-over IVRS call for dacarbazine randomized subjects that enter the Nivolumab Open-Label Extension Phase. Record study drug infusion start and stop times. Refer to Table 4.3-1 for details of study drug administration schedule.</strong></td>
</tr>
<tr>
<td>Administer Study Drug</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
### Table 5.1.2-4: Open-label Procedural Outline (CA209066) Dacarbazine Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>Every 6 Weeks (± 1 Week)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 22</td>
<td>(Refer to Notes)</td>
</tr>
<tr>
<td><strong>Safety Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vital Signs</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Performance Status (ECOG)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Review of Concomitant Medications</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>LFTs, Creatinine</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.1.2-4: Open-label Procedural Outline (CA209066) Dacarbazine Arm

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Each Cycle (Q6 Weeks)</th>
<th>Every 6 Weeks (±1 Week) (Refer to Notes)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy Assessments</td>
<td></td>
<td></td>
<td>Tumor assessments should first be performed every 6 weeks (±1 wk) for the first 12 months from randomization and then every 12 weeks (±1 wk) until disease progression or treatment discontinuation, whichever occurs later. Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline. 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 disease progression is documented.</td>
</tr>
<tr>
<td>Tumor Assessments</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td></td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td></td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td></td>
<td>To be completed to dosing</td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td></td>
<td>To be completed prior to dosing</td>
</tr>
<tr>
<td>Clinical Drug Supplies</td>
<td></td>
<td>X</td>
<td>Record study drug infusion start and stop times. Refer to Table 4.3-1 for details of study drug administration schedule.</td>
</tr>
<tr>
<td>Administer Study Drug</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Table 5.1.2-5: Open-Label Follow-Up Assessments (CA209066) for All Subjects except for subjects previously randomized to Dacarbazine and entering Nivolumab Open-Label Phase

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X, Follow-Up\textsuperscript{a} Visits 1 and 2</th>
<th>Y, Survival Follow-Up\textsuperscript{b} Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td>To assess for potential late emergent study drug related issues</td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td>X</td>
<td>X</td>
<td>For study drug related adverse events only</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td></td>
<td>On site/local CBC w/differential, LFTs, BUN or serum urea level, creatinine, and TSH for X01, repeat at X02 if study drug related toxicity persists.</td>
</tr>
<tr>
<td>Review of Concomitant Medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes Research Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EORTC QLQ C-30</td>
<td>X</td>
<td></td>
<td>Not applicable to subjects previously randomized to Dacarbazine and treated on Nivolumab Open-Label phase. Follow up visits 1 and 2 only</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>X</td>
<td>X</td>
<td>Not applicable to subjects previously randomized to Dacarbazine and treated on Nivolumab Open-Label phase. Follow up visits 1 and 2, and survival visits every 6 months (may be accomplished by visit or phone contact, for Y visits only ).</td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>X</td>
<td></td>
<td>Not applicable to subjects previously randomized to Dacarbazine and treated on Nivolumab Open-Label phase. Follow up visits 1 and 2 only</td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td></td>
<td>Follow up visits 1 and 2 only</td>
</tr>
</tbody>
</table>
Table 5.1.2-5: Open-Label Follow-Up Assessments (CA209066) for All Subjects except for subjects previously randomized to Dacarbazine and entering Nivolumab Open-Label Phase

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X, Follow-Up&lt;sup&gt;a&lt;/sup&gt; Visits 1 and 2</th>
<th>Y, Survival Follow-Up&lt;sup&gt;b&lt;/sup&gt; Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Survival Status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Status</td>
<td>X</td>
<td>X</td>
<td>Every 3 months, may be accomplished by visit (or phone contact for Y visits), to include subsequent anti-cancer therapy</td>
</tr>
<tr>
<td><strong>Efficacy Assessments</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor Assessments</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

Only for subjects without progression on study therapy.

- Patients on nivolumab weight-base, tumor assessments should first be performed at 9 weeks (± 1 wk) following randomization, then every 6 weeks (± 1 wk) thereafter for the first 12 months, and then every 12 weeks from initial study randomization until disease progression is documented.
- Patients who switch to nivolumab flat dose from nivolumab weight base:
  - For patients who have been on nivolumab for a duration ≤12 months, tumor assessments will be done every 6 weeks (± 1 wk) for the first 12 months and then every 12 weeks (± 1 wk) until disease progression is documented.
  - For patients who have been on nivolumab for a duration >12 months, tumor assessments will be done every 12 weeks (± 1 wk) until disease progression is documented.
- For patients on dacarbazine, tumor assessments should be performed at 9 weeks (± 1 wk) following randomization, then every 6 weeks (± 1 wk) for the first 12 months and then every 12 weeks (± 1 wk) until disease progression is documented.
- Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline.
- For responders (CR, PR or SD) on study beyond 2 years, an extension.
Table 5.1.2-5: Open-Label Follow-Up Assessments (CA209066) for All Subjects except for subjects previously randomized to Dacarbazine and entering Nivolumab Open-Label Phase

<table>
<thead>
<tr>
<th>Procedure</th>
<th>X, Follow-Up&lt;sup&gt;a&lt;/sup&gt; Visits 1 and 2</th>
<th>Y, Survival Follow-Up&lt;sup&gt;b&lt;/sup&gt; Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>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 disease progression is documented.</td>
</tr>
</tbody>
</table>

<sup>a</sup> X visits occur as follows - X1 = 30 days from last dose ± 7 days, X2 = 70-84 days from X1. X1 may occur later if treatment has been delayed before discontinuation.

<sup>b</sup> Y, Survival visits continue every 3 months after X visits. BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window.
Table 5.1.2-6: Open-Label Follow-Up Assessments (CA209066) for Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase (Nivolumab Open-Label Extension Phase)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Z, Follow-Up&lt;sup&gt;a&lt;/sup&gt; Visits 1 and 2</th>
<th>Z, Survival Follow-Up&lt;sup&gt;b&lt;/sup&gt; Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted Physical Examination</td>
<td>X</td>
<td></td>
<td>To assess for potential late emergent study drug related issues</td>
</tr>
<tr>
<td>Adverse Events Assessment</td>
<td>X</td>
<td>X</td>
<td>For study drug related adverse events only</td>
</tr>
<tr>
<td>Laboratory Tests</td>
<td>X</td>
<td></td>
<td>On site/local CBC w/differential, LFTs, BUN or serum urea level, creatinine, and TSH for X01, repeat at X02 if study drug related toxicity persists.</td>
</tr>
<tr>
<td>Review of Concomitant Medication</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test (WOCBP only)</td>
<td>X</td>
<td></td>
<td>On site/local Serum or Urine</td>
</tr>
<tr>
<td>Outcomes Research Assessments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health Care Resource Utilization</td>
<td>X</td>
<td></td>
<td>Follow up visits 1 and 2 only</td>
</tr>
<tr>
<td>Survival Status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject Status</td>
<td>X</td>
<td>X</td>
<td>Every 3 months, may be accomplished by visit (or phone contact for Y visits), to include subsequent anti-cancer therapy</td>
</tr>
</tbody>
</table>
### Table 5.1.2-6: Open-Label Follow-Up Assessments (CA209066) for Subjects Previously Randomized to Dacarbazine Entering Nivolumab Open-Label Phase (Nivolumab Open-Label Extension Phase)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Z, Follow-Up(^a) Visits 1 and 2</th>
<th>Z, Survival Follow-Up(^b) Visits</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Assessments</strong></td>
<td>X</td>
<td>X</td>
<td>Only for subjects without progression on study therapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients on nivolumab weight base, tumor assessments should be performed every 6 weeks (± 1 wk) for the first 12 months, and then every 12 weeks until disease progression is documented.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Patients who switch to nivolumab flat dose from nivolumab weight base:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o For patients who have been on nivolumab for a duration ≤12 months, tumor assessments will be done every 6 weeks (± 1 wk) for the first 12 months and then every 12 weeks (± 1 wk) until disease progression is documented.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>o For patients who have been on nivolumab for a duration &gt;12 months, tumor assessments will be done every 12 weeks (± 1 wk) for the first 12 months) until disease progression is documented.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Chest, abdomen, pelvis and all known sites of disease. Use same imaging method as was used at baseline.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 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 disease progression is documented.</td>
</tr>
</tbody>
</table>

\(^a\) Z visits occur as follows - Z01 = 30 days from last dose ± 7 days, Z02 = 70-84 days from Z1. Z1 may occur later if treatment has been delayed before discontinuation.

\(^b\) Z, Survival visits continue every 3 months after Z02 visits. BMS may request that survival data be collected on all randomized subjects outside of the protocol defined window.
5.2 **Study Materials**

The following materials will be provided at study start:

- NCI CTCAE version 4.0;
- BMS-936558 (Nivolumab) Investigator Brochure;
- Pharmacy Binder;
- Laboratory manuals for collection and handling of blood (including biomarker and immunogenicity) and tissue specimens;
- Site manual for operation of interactive voice response system, including enrollment/randomization worksheets;
- Manual for entry of local laboratory data;
- Serious Adverse Events (or eSAE) case report form pages;
- Pregnancy Surveillance Forms;
- RECIST 1.1 pocket guide;
- ePRO manual.

5.3 **Safety Assessments**

At baseline, a medical history will be obtained to capture relevant underlying conditions. The baseline physical examination 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 vital signs and pulse oximetry are to be performed within 3 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 Table 5.1.1-1 and Table 5.1.1-2).

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, endocrine panel (TSH, Free T4, Free T3), glucose and Hep B and C testing (HBV sAg and HCV RNA or HCV antibody test) (see Table 5.1.1-1). 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 each cycle from randomization during study therapy and at the X 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 X follow-up phase (see Table 5.1.1-3) toxicity assessments should be done in person. Once subjects reach the Y or 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 each cycle (except Cycle 1 Day 1) 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 BMS-936558 (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.

**Amendment 09 Update**

For subjects receiving open label nivolumab treatment with flat dose of 480 mg every 4 weeks, local laboratory assessments should be done within 72 hours of the next cycle to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, and LDH at day 1 (see Table 5.1.2-3).

For subjects receiving open label nivolumab treatment with 3 mg/kg every 2 weeks, local laboratory assessments should be done monthly within 72 hours of the dosing to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, and LDH. LFTs should be performed within 72 hours of the week 3 dosing (see Table 5.1.2-2).

For those subjects receiving dacarbazine, local laboratory assessments should be done within 72 hours of the next cycle to include CBC w/differential, LFTs, BUN or serum urea level, creatinine, Ca, Mg, Na, K, Cl, LDH, glucose, TSH (with reflexive free T4/free T3) at day 1. CBC and LFTs are performed within 72 hours of the week 4 dosing (see Table 5.1.2-4).

Additional measures including non-study required laboratory tests should be performed as clinically indicated. Laboratory toxicities (eg, suspected drug induced 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 new cycle for subjects on both treatment arms 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 Appendix 1 of the Investigator’s Brochure.

**5.3.1 Imaging Assessment for the Study**

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

Study evaluations will take place in accordance with the flow charts in Section 5. Baseline assessments should be performed within 28 days prior to the first dose utilizing CT/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 9 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.  

- 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 disease progression is documented.

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 Assessments

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 non-measurable 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 non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.
Non-measurable Lesions

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

5.4.4 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 \( \geq 15 \) 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 (e.g., 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.

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>
<thead>
<tr>
<th>Target Lesions</th>
<th>Non-Target Lesions</th>
<th>New Lesions</th>
<th>Overall Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>CR</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>CR</td>
<td>Non-CR/non-PD</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>CR</td>
<td>Not evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>PR</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>PR</td>
</tr>
<tr>
<td>SD</td>
<td>Non-PD or not all evaluated</td>
<td>No</td>
<td>SD</td>
</tr>
<tr>
<td>Not all evaluated</td>
<td>Non-PD</td>
<td>No</td>
<td>NE</td>
</tr>
<tr>
<td>PD</td>
<td>Any</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>PD</td>
<td>Yes or No</td>
<td>PD</td>
</tr>
<tr>
<td>Any</td>
<td>Any</td>
<td>Yes</td>
<td>PD</td>
</tr>
</tbody>
</table>

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.

**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.

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 RECIST 1.1 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/Immunogenicity Assessments**

Pharmacokinetic blood samples will be drawn at the time points indicated in Table 5.5-1 or Table 5.5-2. Blood samples should be drawn from a site other than the infusion site on days of infusion. All samples collected pre-dose should be taken just prior to the administration (predose) and end-of-infusion (EOI) samples should be taken just prior to EOI (preferably within 2 minutes prior to EOI) from the contralateral arm (ie, the arm not used for the infusion). If the infusion is interrupted, the reason for interruption 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). Only samples collected from subjects receiving BMS-936558...
(Nivolumab) will be analyzed for BMS-936558 (Nivolumab) by a validated ELISA method. Further details on pharmacokinetic sample collection and processing will be provided to the site in a procedure manual.

### Table 5.5-1: Sampling Schedule for BMS-936558 (Nivolumab) or Matched Placebo

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time (Relative to Dosing) Hour</th>
<th>Time (Relative to Dosing) Hour: Min</th>
<th>Pharmacokinetic Blood Sample Schedule&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Immunogenicity Blood Sample Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1D1</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C1D1</td>
<td>1.0 (EOI)</td>
<td>01:00</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>C1D15</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C1D29</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C3D15</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C3D15</td>
<td>1.0 (EOI)</td>
<td>01:00</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Pharmacokinetic blood samples will be collected relative to BMS-936558 (Nivolumab) or BMS-936558 (Nivolumab) Matched Placebo.

<sup>b</sup> EOI: End of Infusion. This sample should be taken immediately prior to stopping the infusion (preferably within 2 minutes prior to the end of infusion). If the end of infusion is delayed to beyond the nominal infusion duration of 1 hour, the collection of this sample should also be delayed accordingly.

**Amendment 07 update**

No pharmacokinetic blood samples will be collected on subjects treated with Dacarbazine and on subjects previously randomized to Dacarbazine and entering the Nivolumab Open-Label Extension Phase.

Subjects randomized to Nivolumab will continue as per schedule described in Table 5.5-1.

**Amendment 09 Update**

Pharmacokinetics and immunogenicity will be collected on all subjects that enter the nivolumab open-label phase with 480 mg every 4 weeks.

### Table 5.5-2: Sampling Schedule for BMS-936558 (Nivolumab) 480 mg flat dose (480 mg every 4 weeks)

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time (Relative to Dosing) Hour</th>
<th>Time (Relative to Dosing) Hour: Min</th>
<th>Pharmacokinetic Blood Sample Schedule&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Immunogenicity Blood Sample Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1D1</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>C2D1</td>
<td>0 (predose)</td>
<td>00:00</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Table 5.5-2: Sampling Schedule for BMS-936558 (Nivolumab) 480 mg flat dose (480 mg every 4 weeks)

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time (Relative to Dosing) Hour: Min</th>
<th>Pharmacokinetic Blood Sample Schedule</th>
<th>Immunogenicity Blood Sample Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Every 3rd Cycle after C2D1 until discontinuation of study treatment</td>
<td>0 (predose) 00:00</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*a* Pharmacokinetic blood samples will be collected relative to BMS-936558 (Nivolumab).

### 5.6 Biomarker Assessments

A variety of factors that could potentially predict clinical response to BMS-936558 (Nivolumab) will be investigated in peripheral blood and in tumor specimens taken from all subjects prior to randomization and as outlined in Table 5.1.1-1 and Table 5.1.1-2. 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 two treatment arms will provide the necessary data to identify and validate biomarkers with predictive vs prognostic value.

**Amendment 07 Update**

Tumor and blood specimens collected from subjects that enter the nivolumab Open-Label phase as outlined in Table 5.1.2-1 and Table 5.1.2-4, will be used to understand the impact of prior dacarbazine treatment on the tumor immune microenvironment and peripheral immune markers. Complete instructions on the collection, processing, handling and shipment of all samples described herein will be provided in a separate procedure manual.

For the Pharmacogenomic information please refer to Pharmacogenomic Amendment 01, as applicable.

#### 5.6.1 Tumor Tissue Specimens

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 or core needle as 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.
In addition, these tumor samples, as well as any tumor samples collected from subjects prior to entering the Nivolumab Open-Label phase may be assessed for the expression of immune or melanoma related genes, RNAs and/or proteins, as well as for 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 BMS-936558 (Nivolumab) and other immunotherapies are currently under investigation. Other methods of tumor PD-L1 expression are being evaluated. Many other tumor tissue biomarkers have the potential to predict for BMS-936558 (Nivolumab) including but not limited to PD-1, PD-L2, tumor infiltrating lymphocytes (TILs) or subpopulations of TILs and a Th1 immune mRNA expression signature.

5.6.2 Serum for Soluble Factors

Blood samples for exploratory serum biomarker analyses will be drawn at the time points indicated in Table 5.5-1 (C1D1, C1D15, C2D1 and C3D1) and Table 5.1.2-2 (C1D1 and C1D15). 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 BMS-936558 (Nivolumab) benefit, correlate with BMS-936558 (Nivolumab) efficacy. Numerous potential serum-based biomarkers are currently under investigation for their potential to predict and/or correlate with efficacy to BMS-936558 (Nivolumab) treatment or treatment or with other immunotherapy agents, 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 Table 5.1.1-2 and Table 5.1.2-2 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 BMS-936558 (Nivolumab) studies.
5.6.4  **Peripheral Blood RNA**

**Amendment 07 Update**

While immunophenotyping of peripheral blood may 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 BMS-936558 (Nivolumab) on immune modulation. Thus, genomic expression patterns of whole blood collected at baseline and during on-treatment as specified in Table 5.1.1-2 and Table 5.1.2-2 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 the T cell repertoire, which may change with BMS-936558 (Nivolumab) treatment or may be predictive of predictive of BMS-936558 (Nivolumab) 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 and other genetic variations in candidate genes that may predispose subjects to BMS-936558 (Nivolumab) benefit or adverse events. 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.

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.

All PRO instruments will be administered during on-study, and follow-up phases as outlined in Table 5.1.1-2 and Table 5.1.1-3, 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 collected in electronic CRF as outlined in Table 5.1.1-2 and Table 5.1.1-3 during screening, on-study, open-label-phase and follow-up phases, respectively.

**Amendment 07 Update**

During open-label phase, the PRO instruments will only be collected for subjects that continue to be treated in the same randomization arm.

Please refer to Table 5.1.2-2 and Table 5.1.2-4.

**Amendment 09 Update**

During Y, Survival Follow-Up Visits, EQ5D is assessed every 6 months (may be accomplished by visit or phone contact).

### 5.8 Other Assessments

#### 5.8.1 Immunogenicity Assessments

Blood samples for immunogenicity analysis will be collected according to the schedule given in Table 5.5-1 and Table 5.5-2. Only samples collected from subjects receiving BMS-936558 (Nivolumab) will be evaluated for development of Anti-Drug Antibody (ADA) by a validated electrochemiluminescent (ECL) immunoassay. Samples may also be analyzed for neutralizing ADA response to nivolumab. (Neutralizing ADA testing conditioned upon validated 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 causal relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

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

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

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

6.1 Serious Adverse Events
A 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 for a minimum of 100 days following the last dose of study treatment. 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/pregnancies through electronic data capture (EDC), electronic submission is the required method for reporting. The paper forms should be used and submitted immediately, only in the event the electronic system is unavailable for transmission. When paper forms are used, the original paper forms are to remain on site.

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

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

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

All SAEs should be followed to resolution or stabilization.

### 6.2 Nonserious Adverse Events

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

#### 6.2.1 Nonserious Adverse Event Collection and Reporting

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

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

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

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

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

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (e.g., 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 (e.g., 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 (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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

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

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

6.5 Overdose

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

6.6 Potential Drug Induced Liver Injury (DILI)

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

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

AND

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

AND

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

6.7 Other Safety Considerations

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

7 DATA MONITORING COMMITTEE AND OTHER EXTERNAL COMMITTEES

A Data Monitoring Committee will be established to provide oversight and safety and efficacy considerations in protocol CA209066 (as this is a Phase 3 randomized, registrational study planning an interim analysis) 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 BMS-936558 (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.

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Determination

The sample size is calculated in order to compare OS between subjects randomized to receive BMS-936558 (Nivolumab) vs dacarbazine. OS will be evaluated for a treatment effect at an overall alpha level of 0.05 (two-sided) with approximately 90% power, accounting for one formal interim analysis to assess efficacy. The number of events and power were calculated assuming an exponential distribution in each arm.

Approximately 410 subjects will be randomized to the two treatment arms in a 1:1 ratio. The study requires at least 312 deaths to ensure approximately 90% power to detect a hazard ratio of 0.69 with an overall type I error of 0.05 (two-sided). The HR of 0.69 corresponds to a 45% increase in the median OS, assuming a median OS of 10 months for dacarbazine and 14.49 months for BMS-936558 (Nivolumab). One formal interim analysis will be conducted (see Section 8.5). The stopping boundaries at the interim and final analyses will be derived based on
the exact number of deaths using Lan-DeMets alpha spending function with O’Brien-Fleming boundaries.

Assuming a constant accrual rate of 43 subjects per month, it will take approximately 30 months to obtain the required number of deaths for the final OS analysis (9.5 months for accrual and 20.5 months for survival follow-up).

8.2 Populations for Analyses

- All enrolled subjects: All subjects who signed an informed consent form and were registered into the IVRS
- All randomized subjects: All subjects who were randomized to any treatment arm in the study.
- All treated subjects: All subjects who received at least one dose of BMS-936558 (Nivolumab) or dacarbazine.
- PK subjects: All subjects with available serum time-concentration data from randomized subjects dosed with BMS-936558 (Nivolumab).
- Immunogenicity subjects: All subjects with available ADA data from randomized subjects dosed with BMS-936558 (Nivolumab).
- 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. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive. OS will be followed continuously while subjects are on the study drug and every 3 months via in-person or phone contact after subjects discontinue the study drug.

8.3.2 Secondary Endpoint(s)

The first secondary objective (to compare PFS) will be measured by the endpoint PFS in all randomized subjects. It is defined as the time from randomization to the date of the first 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 the date they were randomized. Subjects who started any subsequent anti-cancer therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to initiation of the subsequent anti-cancer therapy.

The second secondary objective (to compare ORR) will be measured by the endpoint of ORR in all randomized subjects. 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 arm. 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 therapy, whichever occurs first. For subjects without documented progression or subsequent therapy, all available response designations will contribute to the BOR assessment.

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

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

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

Adverse event assessments and laboratory tests are performed at baseline and continuously throughout the study at the beginning of each subsequent cycle.

The PK objective will be measured from serum concentration. Samples will be collected to characterize pharmacokinetics of BMS-936558 (Nivolumab) and to explore exposure-safety and exposure-efficacy relationships.

Other exploratory endpoints for pharmacogenomics, immunogenicity and outcomes research are discussed in detail in Sections 5.6, 5.7 and 5.8.1.

**8.4 Analyses**

**8.4.1 Demographics and Baseline Characteristics**

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

**8.4.2 Efficacy Analyses**

**8.4.2.1 Primary Endpoint Methods**

The primary analysis of OS in all randomized subjects will be conducted using a two-sided log-rank test stratified by PD-L1 status and M stage. The hazard ratio and corresponding two-sided

Revised Protocol No.: 05
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(1-adjusted $\alpha$)% confidence interval (CI) will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the above factors. OS curves, OS medians with 95% CIs and OS rates at 12 and 24 months with 95% CIs will be estimated using Kaplan-Meier methodology.

### 8.4.2.2 Secondary Endpoint Methods

If OS superiority in all randomized subjects is demonstrated, a gatekeeping testing approach for key secondary endpoints will be applied as described in the statistical analysis plan. Key secondary endpoints include PFS in all subjects and ORR in all randomized subjects.

Analysis of PFS in all randomized subjects will be conducted using a two-sided log-rank test stratified by PD-L1 status and M stage. The hazard ratio and corresponding two-sided (1-adjusted $\alpha$)% confidence interval will be estimated using a Cox proportional hazards model, with treatment arm 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.

Analysis of ORR will be conducted using a Cochran-Mantel Haenszel (CMH) test stratified by the corresponding factors above for all randomized subjects. ORR estimates and corresponding 95% CIs, calculated using the Clopper-Pearson method, will be provided by treatment arm.

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

### 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 arm. All treatment emergent AEs, drug-related AEs, SAEs and drug-related SAEs (will be coded according to MedDRA) and 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 per 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 BMS-936558.
(Nivolumab) and to determine measures of individual exposure (such as steady state peak, trough and time-averaged concentration). Model determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. Result of PK 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 arm. Exploratory analyses may be performed to examine differences between the two arms.

8.4.7 Other Analyses

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

8.5 Interim Analyses

One interim analysis of OS is planned after approximately 218 deaths have been observed (70% of total deaths needed for final analysis) and will be conducted using a two-sided log-rank test stratified by PD-L1 status and M stage. This formal comparison of OS will allow for early stopping for superiority. The timing of this interim analysis was chosen to provide a balance between the maturity and stability of available data and the utility of available data given the timing of the final analysis. The stopping boundaries at the interim and final analyses will be derived based on the exact number of deaths using Lan-DeMets alpha spending function with O'Brien-Fleming boundaries. However, if the interim analysis of OS is performed at exactly 218 events, the study could be stopped for efficacy if the p-value is less than 0.0148 (HR = 0.7180). The nominal significance level for the final OS after 312 events would then be 0.0455 (HR = 0.7966).
In addition to the formal planned interim analysis for OS, the DMC will have access to periodic unblinded interim reports of efficacy and safety to allow a risk/benefit assessment. Details will be included in the DMC charter.

The timing of the final analysis will be revised based on the early stopping of the blinded portion of the study and initiation of the open-label phase.

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.

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 enrolers 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.
## GLOSSARY OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Adverse Reaction</td>
<td>An adverse event that is considered by either the investigator or BMS as related to the investigational product</td>
</tr>
<tr>
<td>Unexpected Adverse Reaction</td>
<td>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)</td>
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<tr>
<td>Serious Adverse Event</td>
<td>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.</td>
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## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AE</td>
<td>adverse event</td>
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<tr>
<td>ALT</td>
<td>alanine aminotransferase</td>
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<td>ANC</td>
<td>absolute neutrophil count</td>
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<tr>
<td>AST</td>
<td>aspartate aminotransferase</td>
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<tr>
<td>AUC(INF)</td>
<td>area under the concentration-time curve from time zero extrapolated to infinite time</td>
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<tr>
<td>BMS</td>
<td>Bristol-Myers Squibb</td>
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<tr>
<td>BP</td>
<td>blood pressure</td>
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<tr>
<td>BUN</td>
<td>blood urea nitrogen</td>
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<td>C</td>
<td>Celsius</td>
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<td>Ca++</td>
<td>calcium</td>
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<tr>
<td>CBC</td>
<td>complete blood count</td>
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<tr>
<td>CFR</td>
<td>Code of Federal Regulations</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>CI^{-}</td>
<td>chloride</td>
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<td>CrCl</td>
<td>creatinine clearance</td>
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<td>cm</td>
<td>centimeter</td>
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<td>Cmax</td>
<td>maximum observed concentration</td>
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<td>CMV</td>
<td>cytomegalovirus</td>
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<td>CNS</td>
<td>central nervous system</td>
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<tr>
<td>CRC</td>
<td>colorectal carcinoma</td>
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<td>CRF</td>
<td>Case Report Form, paper or electronic</td>
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<tr>
<td>CT</td>
<td>computed tomography</td>
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<tr>
<td>CV</td>
<td>coefficient of variation</td>
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<tr>
<td>CYP</td>
<td>cytochrome p-450</td>
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<tr>
<td>DILI</td>
<td>drug-induced liver injury</td>
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<td>dL</td>
<td>Deciliter</td>
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<td>DMC</td>
<td>Data Monitoring Committee</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<td>Term</td>
<td>Definition</td>
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<td>--------------------------------------------</td>
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<tr>
<td>eCRF</td>
<td>Electronic Case Report Form</td>
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<td>EDC</td>
<td>Electronic Data Capture</td>
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<tr>
<td>eg</td>
<td>exempli gratia (for example)</td>
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<tr>
<td>EORTC</td>
<td>European Organisation for Research and Treatment of Cancer</td>
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<tr>
<td>ESMO</td>
<td>European Society for Medical Oncology</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FFPE</td>
<td>formalin-fixed, paraffin-embedded</td>
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<td>FSH</td>
<td>follicle stimulating hormone</td>
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<td>g</td>
<td>Gram</td>
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<td>GCP</td>
<td>Good Clinical Practice</td>
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<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
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<td>HBV</td>
<td>hepatitis B virus</td>
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<tr>
<td>HCG</td>
<td>human chorionic gonadotrophin</td>
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<td>HCV</td>
<td>hepatitis C virus</td>
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<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<td>HR</td>
<td>heart rate</td>
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<tr>
<td>HRT</td>
<td>hormone replacement therapy</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
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<td>ie</td>
<td>id est (that is)</td>
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<tr>
<td>IEC</td>
<td>Independent Ethics Committee</td>
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<tr>
<td>IMP</td>
<td>investigational medicinal products</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug Exemption</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<td>IU</td>
<td>International Unit</td>
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<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>K⁺</td>
<td>Potassium</td>
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<td>kg</td>
<td>Kilogram</td>
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<td>L</td>
<td>Liter</td>
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<tr>
<td>LDH</td>
<td>lactate dehydrogenase</td>
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<td>mg</td>
<td>Milligram</td>
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<td>Term</td>
<td>Definition</td>
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<tr>
<td>Mg</td>
<td>Magnesium</td>
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<tr>
<td>min</td>
<td>Minute</td>
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<td>mL</td>
<td>Milliliter</td>
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<td>mmHg</td>
<td>millimeters of mercury</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>MTD</td>
<td>maximum tolerated dose</td>
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<tr>
<td>μg</td>
<td>Microgram</td>
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<tr>
<td>N</td>
<td>number of subjects or observations</td>
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<tr>
<td>Na</td>
<td>Sodium</td>
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<tr>
<td>N/A</td>
<td>not applicable</td>
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<tr>
<td>ng</td>
<td>nanogram</td>
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<tr>
<td>NIMP</td>
<td>non-investigational medicinal products</td>
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<tr>
<td>NSAID</td>
<td>nonsteroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>NSCLC</td>
<td>non-small cell lung cancer</td>
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<tr>
<td>PBMCs</td>
<td>Peripheral Blood Mononuclear Cells</td>
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<tr>
<td>PD</td>
<td>pharmacodynamics</td>
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<tr>
<td>PD-1</td>
<td>Programmed death receptor - 1</td>
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<tr>
<td>PK</td>
<td>pharmacokinetics</td>
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<tr>
<td>PO</td>
<td>per os (by mouth route of administration)</td>
</tr>
<tr>
<td>PRO</td>
<td>patient reported outcomes</td>
</tr>
<tr>
<td>QD, qd</td>
<td>quaque die, once daily</td>
</tr>
<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire - Core 30</td>
</tr>
<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
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<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SD</td>
<td>standard deviation</td>
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<tr>
<td>SmPC</td>
<td>summary of product characteristics</td>
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<tr>
<td>SOP</td>
<td>standard operating procedures</td>
</tr>
<tr>
<td>T-HALF</td>
<td>half life</td>
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<tr>
<td>Tmax</td>
<td>time of maximum observed concentration</td>
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<tr>
<td>WBC</td>
<td>white blood cell</td>
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<tr>
<td>Term</td>
<td>Definition</td>
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<td>-----------------------------------------------------</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>WOCBP</td>
<td>women of childbearing potential</td>
</tr>
<tr>
<td>WPAI:GH</td>
<td>Work Productivity and Activity Impairment: General Health</td>
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</tbody>
</table>
REFERENCES


5 Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173(2):945-54.


40 Non-Clinical Expedited Safety Report for Nivolumab (BMS-936558) (Ad Hoc CARES #54344.1); BMS DCN 930067627 1.0.


## APPENDIX 1  M STAGE CATEGORIES FOR CUTANEOUS MELANOMA

### Table 1: M Stage Categories for Cutaneous Melanoma\(^a\)

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>Not applicable</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous, or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
<td>Elevated</td>
</tr>
</tbody>
</table>


\(^b\) LDH - Lactate dehydrogenase
## APPENDIX 2 PERFORMANCE STATUS SCALES

### ECOG PERFORMANCE STATUS

<table>
<thead>
<tr>
<th>Grade</th>
<th>ECOG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

---

APPENDIX 3 GUIDANCE ON CONTRACEPTION

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

(CHOSE ONE OF THE FOLLOWING 3 OPTIONS)

OPTION 1: Any TWO of the following methods
- Hormonal methods of contraception
- IUD
- Vasectomy
- Tubal Ligation
- A Barrier method (Female or Male Condom with spermicide, Cervical Cap with spermicide, Diaphragm with spermicide)

OPTION 2: Male condom (with spermicide) and diaphragm

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

a The theoretical failure rate for any of the options listed is considerably less than 1% per year
b Excludes progestin-only pills
c Hormonal contraceptives may not be used for contraception unless a drug-drug interaction study has demonstrated that the pharmacokinetics of the hormone based contraceptive has not been adversely affected by the investigational drug in the protocol or there is compelling evidence to substantiate that investigational product(s) or con-meds will not adversely affect contraception effectiveness. The PK scientist and MST chair must agree that the use of hormone-based contraception is safe and efficacious for WOCBP. The use of hormone-based contraceptives is not otherwise restricted
d A highly effective method of birth control with a failure rate less than 1% per year
e IUDs used should have a failure rate less than 1% (highly effective method), such as Mirena and ParaGard
f Must be at least 90 days from date of surgery with a semen analysis documenting azoospermia
g These 2 barrier methods together are acceptable for a teratogenic drug

UNACCEPTABLE METHODS OF CONTRACEPTION

Abstinence (including periodic abstinence)
No method
Withdrawal
Rhythm
Vaginal Sponge
Any barrier method without spermicide
Spermicide
Progestin only pills
Concomitant use of female and male condom
In countries where spermicide is not available or its use is not considered compatible with male condoms, use of a male condom without spermicide in conjunction with a hormonal method, IUD, or tubal ligation will be acceptable to fulfill this recommendation. Any barrier method when used alone (without spermicide) or the concomitant use of a female and male condom, is not considered a sufficient method of contraception, as each carries a failure rate of > 1%.

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

**Grade 1**  
Diarrhea: < 4 stools/day over baseline; Colitis: asymptomatic

**Management**
- Continue I-O therapy per protocol
- Symptomatic treatment

**Follow-up**
- 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

**Management**
- Delay I-O therapy per protocol
- Symptomatic treatment

**Follow-up**
- 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

**Management**
- 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

**Follow-up**
- 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)

**Grade 1**
Creatinine > ULN and > than baseline but ≤ 1.5x baseline

- *Continue I-O therapy per protocol*
- *Monitor creatinine weekly*

**Management**

**Follow-up**
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*

**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, 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*

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.

Grade of Pneumonitis (NCI CTCAE v4)

Grade 1
Radiographic changes only
- Consider delay of I-O therapy
- Monitor for symptoms every 2-3 days
- Consider Pulmonary and ID consults

Grade 2
Mild to moderate new symptoms
- Delay I-O therapy per protocol
- Pulmonary and ID consults
- Monitor symptoms daily, consider hospitalization
- 1.0 mg/kg/day methylprednisolone IV or oral equivalent
- Consider bronchoscopy, lung biopsy

Grade 3-4
Severe new symptoms; New/worsening hypoxia; Life-threatening
- Discontinue I-O therapy per protocol
- Hospitalize
- Pulmonary and ID consults
- 2-4 mg/kg/day methylprednisolone IV or IV equivalent
- Add prophylactic antibiotics for opportunistic infections
- Consider bronchoscopy, lung biopsy

Management

Follow-up
- Re-image at least every 3 weeks
  If worsens:
  - Treat as Grade 2 or 3-4
- Re-image every 1-3 days
  If improves:
  - When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics
  - If not improving after 2 weeks or worsening:
    - Treat as Grade 3-4
- If improves to baseline:
  - Taper steroids over at least 6 weeks
  - If not improving after 48 hours or worsening:
    - Add additional immunosuppression

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)

- **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
- **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
- **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

**Management**

- Continue LFT monitoring per protocol
- If worsens:
  - Treat as Grade 2 or 3-4
- 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
- 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.

Asymptomatic TSH elevation
- Continue I-O therapy per protocol
- If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult

Symptomatic endocrinopathy
- Evaluate endocrine function
- Consider pituitary scan
- Symptomatic with abnormal lab/pituitary scan:
  - Delay I-O therapy per protocol
  - 1-2 mg/kg/day methylprednisolone IV or PO equivalent
  - Initiate appropriate hormone therapy
- No abnormal lab/pituitary MRI scan but symptoms persist:
  - Repeat labs in 1-3 weeks / MRI in 1 month
- If improves (with or without hormone replacement):
  - Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections
  - Resume I-O therapy per protocol
  - Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)
- Delay or discontinue I-O therapy per protocol
- Rule out sepsis
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids
- Consult endocrinologist
- If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy

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.

**Grade of Rash**
(NCI CTCAE v4)

**Grade 1-2**
Covering ≤ 30% BSA
- Symptomatic therapy (e.g. antihistamines, topical steroids)
- Continue I-O therapy per protocol

**Grade 3-4**
Covering >30% BSA; Life threatening consequences**^**
- Delay or discontinue I-O therapy per protocol
- Consider skin biopsy
- Dermatology consult
- 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent

**Management**

**Follow-up**

If persists > 1-2 weeks or recurs:
- Consider skin biopsy
- Delay I-O therapy per protocol
- Consider 0.5-1.0 mg/kg/day methylprednisolone IV or oral equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
If worsens:
- Treat as Grade 3-4

If improves to Grade 1:
- Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
- Resume I-O therapy per protocol

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.
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)

Grade 1
Asymptomatic or mild symptoms; Intervention not indicated
- Continue I-O therapy per protocol

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

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

Management

Follow-up

Continue to monitor the patient.
If worsens:
- Treat as Grade 2 or 3-4

If improves to baseline:
- Resume I-O therapy per protocol when improved to baseline
If worsens:
- Treat as Grade 3-4

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